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IMAGERIE MULTIMODALE DES CORRÉLATS VASCULAIRES DU VIEILLISSEMENT CÉRÉBRAL

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présentée par : DESJARDINS Michèle

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a été dûment acceptée par le jury d'examen constitué de :

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RÉSUMÉ

Plusieurs décennies de recherche ont permis de démontrer que le vieillissement a des effets sur une multitudes de composantes du cerveau. En particulier, des preuves s'accumulent à l'effet qu'il existe un lien entre le fonctionnement du cerveau au niveau cognitif et la santé du système vasculaire, notamment le débit sanguin cérébral (DSC) qui diminue avec l'âge, ainsi que la santé cardiorespiratoire qui pourrait corréler à la performance cognitive selon certaines études. Plusieurs techniques d'imagerie cérébrale couramment utilisées en recherche, telles que le signal dépendant du niveau d'oxygénation du sang en imagerie par résonance magnétique (BOLD-IRM), se basent sur les corrélats vasculaires de l'activité des neurones. Cela en fait des outils propices pour l'étude des effets vasculaires du vieillissement, qui influencent directement les signaux mesurés. Cette thèse a utilisé plusieurs techniques d'imagerie cérébrale basées sur l'hémodynamique pour étudier les effets du vieillissement sur le cerveau à différentes échelles spatiales, chez l'humain et dans un modèle animal chez le rat. Dans un premier temps, la microscopie biphotonique a été utilisée pour mesurer la vitesse des globules rouges, le diamètre et la densité des capillaires ainsi que l'hématocrite local dans près de 1000 capillaires chez 12 rats Long-Evans jeunes (3 mois) et 12 rats âgés (24 mois) anesthésiés. Il a été mesuré que la vitesse des globules rouges et le diamètre étaient plus élevés dans les capillaires de rats âgés (par 48 et 7% respectivement), tandis que l'hématocrite et la densité volumiques des capillaires étaient plus faibles (par 32 et 20%). Ces résultats suggèrent que la diminution du DSC avec l'âge serait surtout attribuable à une baisse de densité vasculaire. En second lieu, l'IRM et la spectroscopie résolue en temps de vol ont permis de mesurer le débit, l'oxygénation (sO_2) et la concentration totale d'hémoglobine (HbT) dans les cerveaux d'humains jeunes (18-30 ans) et âgés (62-72 ans), en plus de la réponse à une tâche cognitive de Stroop en termes de BOLD et de DSC. La capacité cardiorespiratoire des sujets et été mesurée par un test de VO_{2max}. Nous avons mesuré, dans le cortex préfrontal gauche sollicité par la tâche de Stroop, des valeurs plus faibles de DSC (par 19%), sO_2 (par 6%) et HbT (par 21%) chez les sujets âgés. Dans le groupe âgé, les mesures de sO_2 étaient corrélées à la performance cognitive dans la tâche Stroop ainsi qu'au VO_{2max}, mais pas celles de DSC ni de HbT. Ces résultats suggèrent un effet protecteur de l'exercice physique sur la santé cognitive dans le vieillissement, dont les mécanismes seraient liés à une amélioration de l'oxygénation cérébrale. Enfin, les mêmes groupes de rats jeune et âgé ont été soumis à un stimulus vasodilatateur, l'hypercapnie, afin de mesurer la réponse hémodynamique à l'aide de

plusieurs modalités d'imagerie. Les mesures ont démontré une diminution de la réponse hémodynamique à l'hypercapnie en termes de DSC, de HbT et de HbO (hémoglobine oxygénée) chez les rats âgés, suggérant une diminution de la réactivité vasculaire. La compliance des vaisseaux pourrait aussi être réduite avec l'âge puisque le rapport des réponses Δvolume/Δdébit était plus faible chez les rats âgés. En conclusion, les travaux menés dans cette thèse permettent d'approfondir notre compréhension des mécanismes du vieillissement et d'en isoler certains aspects vasculaires. Les résultats démontrent l'importance de considérer les différences vasculaires dans l'interprétation de mesures de neuroimagerie basées sur l'hémodynamique dans les études du vieillissement.

ABSTRACT

Several decades of research have demonstrated that aging affects a multitude of components in the brain. In particular, evidence is accumulating on the relation between brain function and vascular health, including cerebral blood flow (CBF), which decreases with age, and cardiopulmonary health which could correlate with cognitive performance according to some studies. Several brain imaging techniques commonly used in research, such as the blood oxygenation level dependent signal in magnetic resonance imaging (BOLD-MRI), are based on the vascular correlates of neural activity. This makes them suitable tools for the study of the vascular effects of aging, which directly influence the measured signals. This thesis used several imaging modalities based on hemodynamics to study the effects of aging on the brain at different spatial scales, in humans and in an animal model, the rat. Initially, two-photon microscopy was used to measure the velocity of red blood cells (RBCs), the diameter and the density of capillaries and the local hematocrit in nearly 1000 capillaries in 12 young (3 months-old) and 12 aged anesthetized Long-Evans rats (24 months-old). We measured higher RBCs velocity and diameter in the capillaries of aged rats (by 48 and 7 % respectively), while the hematocrit and volumetric capillary density were lower (by 32 and 20 %). These results suggest that the decrease in CBF with age is due primarily to a decrease in vascular density. Second, MRI and time-resolved spectroscopy were used to measure the CBF, oxygenation (sO_2) and total hemoglobin concentration (HbT) in the brains of young (18-30 years-old) and elderly (62-72 years-old) humans, in addition to the response to a cognitive Stroop task in terms of BOLD and CBF. Cardiorespiratory fitness was measured by a VO_{2max} test. In the left prefrontal cortex activated by the Stroop task, we measured lower values of CBF (by 19%), sO_2 (by 6%) and HbT (by 21%) in the elderly. In the older group, measures of sO_2 were correlated with Stroop task cognitive performance and with VO_{2max}, while CBF and HbT were not. These results suggest a protective effect of physical activity on cognitive health in aging, mediated by an improvement in cerebral oxygenation. Finally, the same groups of young and old rats were subjected to a vasodilating stimulus, hypercapnia, for measuring the hemodynamic response with several imaging modalities. The data demonstrated a decrease in the hemodynamic response to hypercapnia in terms of CBF, HbT and HbO (oxygenated hemoglobin) in aged rats, suggesting decreased vascular reactivity. The vessels' compliance could also be reduced with age, as the ratio of

Δvolume/Δflow response amplitudes was lower in aged rats. In conclusion, the work presented in this thesis helps to deepen our understanding of the mechanisms of aging and to isolate certain of its vascular aspects. The results demonstrate the importance of considering vascular differences in the interpretation of neuroimaging measures based on hemodynamics in studies of aging.

TABLE DES MATIÈRES

LISTE DES TABLEAUX

LISTE DES FIGURES

LISTE DES ANNEXES

LISTE DES SIGLES ET ABRÉVIATIONS

$_0$ (indice)	À l'état de repos
ASL	*Arterial spin labelling*
BOLD	*Blood oxyenation level dependent*
$CMRO_2$	Taux du métabolisme cérébral de l'oxygène (*cerebral metabolic rate of oxygen*)
DSC	Débit sanguin cérébral
FGL	Fluxmétrie par granularité laser
HbO	Hémoglobine oxygénée
HbR	Hémoglobine déosygénée
HbT	Hémoglobine totale (HbO + HbR)
IOD	Acide désoxyribonucléique
IRM(f)	Imagerie par résonance magnétique (fonctionnelle)
MBP	Microscopie biphotonique
sO_2	Saturation en oxygène
SRT	Spectroscopie résolue en temps de vol
VO_{2max}	Consommation maximale d'oxygène (durant l'exercice physique)

INTRODUCTION

1.1 Contexte et problématique

Depuis trois décennies, notre capacité à sonder l'activité cérébrale humaine a significativement évolué grâce aux progrès en imagerie peu ou pas invasive, notamment l'imagerie par résonance magnétique fonctionnelle (IRMf). La technique d'IRMf la plus répandue, appelée BOLD (de l'anglais *Blood Oxygenation Level Dependent*), est largement utilisée dans la recherche en neurosciences pour cartographier des régions du cerveau sollicitées par divers stimuli, comparer des populations et étudier des pathologies. Toutefois, dans le BOLD comme dans d'autres techniques d'imagerie dites hémodynamiques, les mesures sont indirectes et résultent d'interactions entre des phénomènes électriques, métaboliques et vasculaires dans le cerveau. Or, ces interactions, baptisées « couplage neuro-vasculaire », demeurent mal connues et constituent encore aujourd'hui un domaine de recherche en elles-mêmes. En outre, la variabilité de la physiologie cérébrale complique la généralisation des résultats, en particulier dans l'étude de populations très hétérogènes.

La proportion âgée de 65 ans et plus de la population du Québec a plus que doublé entre 1971 et 2011 et devrait à nouveau presque doubler d'ici 2051 (Banque de données des statistiques officielles sur le Québec, s. d.). Dans le contexte démographique actuel, les conséquences sociales et économiques du vieillissement prennent une importance grandissante. Une meilleure compréhension des mécanismes du vieillissement s'impose donc pour améliorer la qualité de vie d'une portion croissante de la population. Le vieillissement a des conséquences diverses sur beaucoup d'aspects de la santé, des échelles cellulaire à systémique. Entre autres, plusieurs observations démontrent des effets du vieillissement sur les vaisseaux sanguins et la dynamique du débit sanguin. Ces effets sont susceptibles de moduler les signaux d'imagerie cérébrale basés sur l'hémodynamique, faisant des aînés une population très hétérogène pour la recherche en neuroimagerie.

En effet, plusieurs pathologies cérébrales associées au vieillissement ont des corrélats vasculaires connus, par exemple les démences vasculaires et la maladie d'Alzheimer. Même dans le vieillissement non-pathologique, le déclin cognitif a été associé à une diminution de la perfusion dans certaines régions cérébrales. Il reste toutefois à établir si les changements vasculaires sont

causes ou conséquences de changements au niveau des neurones. Il semble donc y avoir un lien étroit entre le vieillissement cognitif et les changements vasculaires avec l'âge. Dans ce contexte, cette thèse fait usage de méthodes d'imagerie basées sur l'hémodynamique pour étudier plusieurs corrélats vasculaires du vieillissement dans le cerveau.

Lorsqu'une région du cerveau s'active, par exemple en réponse à un stimulus, une série d'événements est déclenchée, à différentes échelles spatiales et temporelles. L'activation des neurones et des astrocytes pour la génération et la transmission des influx nerveux crée une dépense énergétique qui nécessite l'apport d'oxygène et de glucose par le sang. S'ensuivent l'augmentation de la consommation d'oxygène et de glucose, ainsi que du débit sanguin, ce qui augmente localement le volume sanguin et le niveau d'oxygénation du sang; cascade d'événements regroupés sous le nom de « réponse hémodynamique ». Différents éléments de la réponse hémodynamique sont autant de cibles pour des techniques d'imagerie dites fonctionnelles, visant à mesurer l'activité neuronale via ses corrélats hémodynamiques (voir Figure 1-1). L'interprétation de telles mesures d'imagerie repose donc sur des hypothèses fondamentales sur la nature du couplage neuro-vasculaire, pourtant encore sujet actif de recherche à ce jour. En particulier, plusieurs résultats portent à croire que le couplage neuro-vasculaire pourrait être affecté par certaines conditions ou pathologies, dont le vieillissement. Il est donc primordial de mieux comprendre l'effet du vieillissement sur les mesures hémodynamiques.

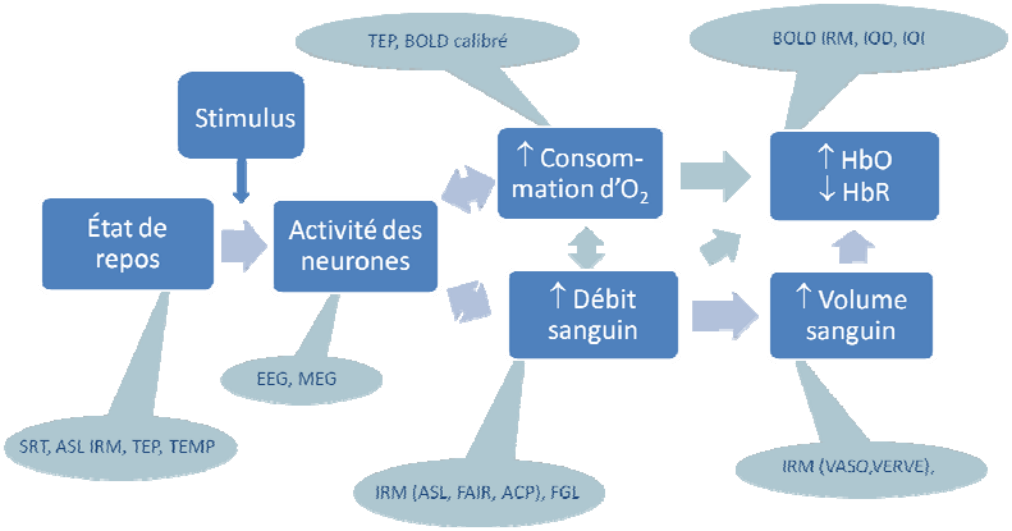

Figure. 1-1. Schéma de la cascade d'événements constituant la réponse hémodynamique et exemples de techniques d'imagerie fonctionnelle se basant sur ses différentes étapes. HbO : hémoglobine oxygénée; HbR : hémoglobine désoxygénée. SRT : spectroscopie résolue en temps de vol; IRM : imagerie par résonance magnétique; ASL IRM : marquage des spins artériels (nom de la séquence IRM de l'anglais *arterial spin labelling*); TEP : tomographie par émission de positrons; TEMP : tomographie d'émission monophotonique; EEG : électro-encéphalographie; MEG : magnéto-encéphalographie; FAIR IRM : inversion-récupération alternées sensibles au débit (nom de la séquence IRM de l'anglais *flow sensitive alternating inversion recovery*); ACP IRM : angiographie par contraste de phase; FGL : fluxmétrie par granularité laser; BOLD IRM: signal dépendant du niveau d'oxygénation du sang (nom de la séquence IRM de l'anglais *blood oxygen level dependent*); IOD : imagerie optique diffuse; IOI : imagerie optique intrinsèque; VASO IRM : occupation du volume vasculaire (de l'anglais *vascular space occupancy*); VERVE IRM : réalignement veineux pour estimation du volume (de l'anglais *venous-refocusing for volume-estimation*).

La neuroimagerie fonctionnelle désigne les techniques d'imagerie visant à mesurer des changements évoqués dans le cerveau par un stimulus ou une tâche. Le signal IRMf-BOLD est de loin le plus répandu. Ce dernier repose sur les propriétés magnétiques de la molécule d'hémoglobine, qui est diamagnétique dans sa forme oxygénée (HbO), mais paramagnétique dans sa forme désoxygénée (HbR). La présence de molécules d'HbR perturbe localement le champ magnétique, ce qui modifie le temps de relaxation transversale T_2 ou T_2*. L'amplitude du signal IRM mesuré à un temps d'écho (TE) donné dépend donc de la présence d'HbR, qui elle-même dépend de la cascade de la réponse hémodynamique: l'augmentation du métabolisme d'oxygène par les cellules cérébrales tend à augmenter la quantité d'HbR, tandis que l'afflux sanguin local amène plus d'HbO et dilue l'HbR. Globalement, une augmentation d'activité neurale est typiquement - bien que plusieurs cas particuliers diffèrent - corrélée avec une diminution de la concentration d'HbR, ce qui se manifeste par une augmentation du signal BOLD.

Par contre, il est évident que si la perfusion ou l'oxygénation au repos, ou alors le rapport entre l'augmentation du métabolisme et de la perfusion, diffèrent, alors une même réponse neuronale donnera lieu à des amplitudes différentes du signal BOLD. Or, un nombre croissant d'études démontrent que dans diverses conditions, par exemple le vieillissement, les déterminants du signal IRMf sont affectés si bien qu'on ne peut interpréter une différence de signal BOLD comme

une différence d'activité neuronale (Gauthier et al, 2013; Parkes et al., 2012; Ances et al., 2009). Cela pourrait remettre en question plusieurs théories sur le vieillissement dérivées de résultats ayant été interprétés en se basant sur cette hypothèse. Ainsi, pour étudier un phénomène tel que le vieillissement, il importe de quantifier son effet sur les déterminants du signal, afin de pouvoir interpréter correctement les changements mesurés. C'est là une motivation fondamentale de cette thèse.

L' influence vasculaire sur le signal BOLD, qui pour plusieurs chercheurs constituait, au mieux, une hypothèse et, au pire, un handicap, nous avons choisi de l'exploiter comme un outil dans ces travaux afin d'explorer des questions vasculaires. Les hypothèses centrales de ce projet s'ancrent donc autour de deux observations principales. D'une part, l'influence de la physiologie vasculaire sur les mesures d'imagerie fonctionnelle hémodynamiques, et d'autre part, le lien apparent entre cognition et santé vasculaire dans le vieillissement.

1.2 Objectifs, hypothèses, démarche de l'ensemble du travail de recherche et organisation générale du document

Étant donné ce contexte, le ***postulat central*** de cette thèse est le suivant : la combinaison de méthodes d'imagerie basées sur l'hémodynamique permet d'approfondir la connaissance des effets du vieillissement sur le cerveau, qui sont en partie de nature vasculaire.

Ce projet vise à éclaircir les mécanismes du vieillissement cérébral et à améliorer l'interprétation des mesures d'imagerie appliquées à cette question. Si l'objet d'étude ultime est le cerveau humain, l'utilisation de modèles animaux permet une exploration contrôlée, précise et directe de mécanismes complexes à l'échelle microscopique par l'utilisation de méthodes d'imagerie invasives. En particulier, une proportion significative du signal BOLD provenant des capillaires (Boxerman, Hamberg, Rosen, & Weisskoff, 1995; Pathak, Ward, & Schmainda, 2008), lieu d'échange de la circulation sanguine avec les cellules nerveuses, ces vaisseaux revêtent une importance toute particulière dans la compréhension des mécanismes cérébraux qui sous-tendent le BOLD. Ainsi, la première étape de notre travail a été de mesurer les effets du vieillissement sur le débit dans les capillaires, afin de mieux comprendre les mesures macroscopiques du débit et du BOLD, telles que celles réalisées dans le second article. Ce dernier, coeur de cette thèse, s'est intéressé directement à divers corrélats vasculaires du vieillissement chez des sujets humains.

Ce second article ayant notamment démontré des différences dans la réponse BOLD entre les groupes d'âge, telles que souvent observées aussi dans la littérature, la troisième étude a servi à explorer plus à fond la contribution vasculaire à cette différence. Pour ce faire, la réponse hémodynamique a été mesurée en réponse à un stimulus vasodilatateur, l'hypercapnie, reconnu pour susciter une augmentation du débit partout dans le cerveau, sans modifier le métabolisme cérébral (T. L. Davis, Kwong, Weisskoff, & Rosen, 1998; Hoge et al., 1999a). Ainsi, dans ce troisième article, la combinaison de multiples techniques d'imagerie fonctionnelle a permis d'obtenir des mesures complémentaires, à différentes échelles spatiales et temporelles (voir Figure 1-2), de la réponse hémodynamique. Cette étude finale vient donc aussi complémenter le travail d'exploration des effets du vieillissement à plusieurs échelles.

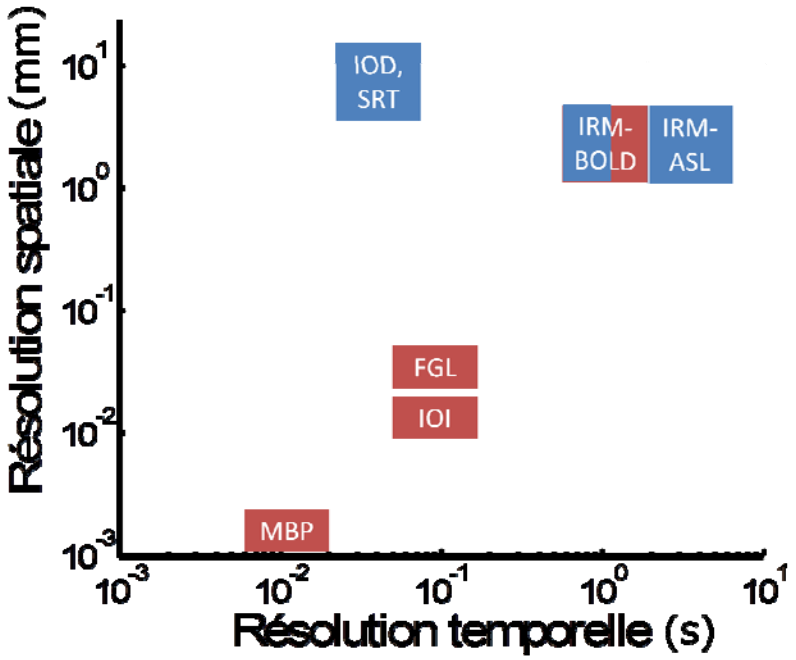

Figure 1-2: Comparaison de la résolution temporelle et spatiale de différentes techniques d'imagerie cérébrale utilisées dans cette thèse. En rouge, les techniques invasives utilisées chez le rat; en bleu, les techniques non-invasives utilisées chez l'humain. IOD: imagerie optique diffuse; SRT: spectroscopie résolue en temps de vol; IRM: imagerie par résonance magnétique; BOLD IRM: signal dépendant du niveau d'oxygénation du sang (nom de la séquence IRM de l'anglais *blood oxygenation level dependent*); ASL IRM: marquage des spins artériels (nom de la séquence IRM de l'anglais *arterial spin labelling*); IOI: imagerie optique intrinsèque; FGL: fluxmétrie par granularité laser; MBP: microscopie biphotonique.

L'***objectif général*** de cette thèse est donc 1) d'approfondir la compréhension des mécanismes par lesquels le vieillissement affecte la vasculature cérébrale aux niveaux microscopique et macroscopique, et 2) de raffiner l'interprétation des techniques de mesure disponibles pour permettre d'atteindre ce but. Les objectifs spécifiques se détaillent en trois étapes:

Objectif 1 : À l'échelle microscopique, mesurer l'effet du vieillissement sur le débit sanguin dans les capillaires cérébraux dans un modèle animal, en mesurant a) la vitesse des globules rouges, b) le diamètre des capillaires, c) l'hématocrite local, à l'état de repos;

Hypothèses : Étant donné que le débit sanguin cérébral diminue à l'échelle macroscopique avec le vieillissement, nous avons fait l'hypothèse que a) la vitesse et b) le diamètre des vaisseaux seraient plus faibles chez les rats âgés. Nous avons aussi fait l'hypothèse que c) l'hématocrite local diminuerait avec l'âge.

Article : **Desjardins, M**., Berti, R., Lefebvre, J., Dubeau, S. et Lesage, F. Aging-related differences in cerebral capillary blood flow in anesthetized rats. Neurobiology of Aging. 30 pages, soumis le 15 juillet 2013.

Objectif 2 : À l'échelle humaine, investiguer les corrélats vasculaires du vieillissement cognitif en mesurant chez des sujets jeunes et âgés a) la perfusion communément appelée débit sanguin cérébral de base (DSC_0)[1], b) la concentration totale d'hémoglobine régionale (HbT_0), c) l'oxygénation sanguine cérébrale régionale (sO_{20}), d) la consommation maximale d'oxygène (VO_2max), indicateur de la condition cardiorespiratoire, e) la performance cognitive dans une tâche de Stroop, f) la réponse hémodynamique en IRM-BOLD à la tâche cognitive, f) la force de la connectivité (connectivité fonctionnelle) entre les régions du cerveau à l'état de repos.

Hypothèses : Tel que mesuré précédemment dans la littérature, le débit sanguin cérébral diminuera avec l'âge. Bien que jamais mesurées auparavant, nous avons fait l'hypothèse que la

[1] Le terme « débit sanguin cérébral » (*cerebral blood flow*) est couramment employé pour désigner la perfusion, qui est la quantité véritablement mesurée par la technique d'IRMf-ASL utilisée dans cette thèse chez l'humain. La différence est qu'un débit représente des unités de volume / temps (de sang traversant un vaisseau), tandis que la perfusion (d'un organe, d'une région donnée) est en fait un débit par unité de masse ou de volume (de l'organe étudié). Voir à ce sujet un paragraphe de la section 7.1 de la discussion. Dans cette thèse, l'acronyme DSC est utilisé pour désigner la perfusion, en accord avec la convention de la littérature qui utilise alternativement *perfusion* et *CBF*.

concentration d'hémoglobine ainsi que l'oxygénation diminueraient aussi étant donné la raréfaction des vaisseaux sanguins et la diminution du métabolisme cérébral rapportées dans la littérature. Le VO_2max diminuera aussi avec l'âge, tout comme la performance cognitive. Nous avons aussi vérifié l'hypothèse selon laquelle la performance cognitive est corrélée au VO_2max (les individus en meilleure forme cardiorespiratoire étant moins affectés par le déclin cognitif). Enfin, nous avons fait l'hypothèse que des différences dans le signal IRMf-BOLD ainsi que dans les valeurs de DSC_0, HbT_0 et sO_{20} seraient des corrélats de la différence de performance cognitive avec l'âge et avec le VO_2max.

Article : **Desjardins, M.**, Pouliot, P., Perlbarg, V., Desjardins-Crépeau, L., Gauthier, C., Leclerc, P. O., Hoge, R., Bherer, L., Benali, H. et Lesage, F. (2013) Association of cardiovascular fitness with cognition, cerebral blood flow and oxygenation in aging. NeuroImage. 25 pages, soumis le 1er octobre 2013.

Objectif 3 : Mettre en évidence les aspects vasculaires de l'effet du vieillissement sur le signal BOLD en mesurant la réponse hémodynamique à un stimulus vasodilatateur, l'hypercapnie, dans deux groupes de rats jeunes et âgés, avec plusieurs modalités d'imagerie donnant: a) le signal IRMf-BOLD, b) le changement de débit, c) le changement de concentrations d'HbO, HbR et HbT, et d) le débit dans les artérioles et veinules individuelles.

Hypothèses : Suivant les résultats d'études du vieillissement faites par nos collègues utilisant d'autres stimuli (Dubeau, Ferland, Gaudreau, Beaumont, & Lesage, 2011) ou dans d'autres espèces (Gauthier et al., 2013), nous avons fait l'hypothèse que les réponses hémodynamiques seraient plus faibles chez les sujets âgés.

Article : **Desjardins, M**., Berti, R., Pouliot, P., Dubeau, S. et Lesage, F. Multimodal study of the hemodynamic response to hypercapnia in anesthetized aged rats. Neuroscience letters. 15 pages, soumis le 24 novembre 2013.

En parallèle, des travaux auxiliaires menés en collaboration durant cette thèse ont permis d'autres publications :

Article de revue de littérature sur la méthode d'imagerie optique diffuse (IOD) et ses applications, co-écrit par les 3 auteurs : **Desjardins, M.**, Pouliot, P. et Lesage, F. (2012) Principles and

application of diffuse optical imaging for the brain. Current Medical Imaging Reviews, 8(3): 157-173.

Article sur le vieillissement chez l'humain utilisant une partie des données de l'article 2) ainsi qu'un ensemble de programmes d'analyses de données IRMf-ASL écrits par moi : Amiri, M., Pouliot, P., Bonnéry, C., Leclerc, P.-O., **Desjardins, M.** , Lesage, F. et Joanette, Y. (2013) fNIRS Exploration of the Hemodynamic Changes Allowing for the Semantic Processing of Words in Normal Aging. Journal of Gerontology: Psychological Sciences, 29 pages, soumis le 23 octobre 2013.

Article utilisant une partie des données de l'article 2) ainsi qu'un travail de modélisation de la propagation des photons en IOD auquel j'ai participé : Bonnery, C., Leclerc, P.O., **Desjardins, M.**, Bherer, L., Hoge, R., Pouliot, P. et Lesage, F. (2012) Changes in diffusion path length with old age in diffuse optical tomography. Journal of Biomedical Optics. 17(5): 056002.

Article appliquant l'IOD à une étude cognitive du vieillissement, pour laquelle j'ai contribué à la planifications des acquisitions de données et créé les programmes d'analyses : Gagnon, C., Desjardins-Crépeau, L., Tournier, I., **Desjardins, M.**, Lesage, F., Greenwood, C. et Bherer, L. (2012) Near-infrared imaging of the effects of glucose ingestion and regulation on prefrontal activation during dual-task execution in healthy fasting older adults. Behavioural Brain Research, 232(1): 137-147.

Article appliquant un modèle biophysique que j'ai implémenté à l'étude du vieillissement chez le rat : Dubeau, S., **Desjardins, M.**, Pouliot, P., Beaumont, E., Gaudreau, P. et Ferland, G. (2011) Biophysical model estimation of neurovascular parameters in a rat model of healthy aging. NeuroImage. 57(4): 1480-1491.

CHAPITRE 2 REVUE CRITIQUE DE LA LITTÉRATURE

2.1 Le vieillissement

Le vieillissement normal est associé à divers changements métaboliques et vasculaires, à la fois systémiques et spécifiques à certains organes. Dans le cerveau, la structure et la fonction sont modifiées avec l'âge. Bien que des corrélations aient été observées entre cognition et perfusion, les mécanismes spécifiques du déclin cognitif restent méconnus et pourraient être multiples.

2.1.1 Le vieillissement cérébral chez l'humain

2.1.1.1 Changements liés à l'âge dans la physiologie vasculaire cérébrale

Élucider les mécanismes du vieillissement cérébral a fait l'objet d'une grande quantité d'études. Le vieillissement a été associée à une diminution du métabolisme de glucose (CMRglc) et d'oxygène ($CMRO_2$) mesurés par tomographie par émission de positrons (TEP), (Leenders et al., 1990a; Marchal et al., 1992), bien que cette conclusion soit controversée (Bentourkia et al., 2000a; Tumeh et al., 2007a). Chez l'homme, le débit sanguin cérébral de base (DSC_0) semblerait diminuer avec l'âge, mais pas toujours de façon linéaire, selon des études utilisant l'IRM (Ances et al., 2009a; Asllani et al., 2009a; Biagi et al., 2007a; Restom, Bangen, Bondi, Perthen, & Liu, 2007), la tomographie d'émission monophotonique (TEMP) (Slosman et al., 2001a) et la TEP (Bentourkia et al., 2000a; Leenders et al., 1990a). L'atrophie du cerveau causée par un amincissement cortical et une hypertrophie ventriculaire, ainsi qu'une baisse du volume sanguin cérébral (VSC) (Leenders et al., 1990a; Y. Zhang, Peng, Chen, & Chen, 2010a) ont également été signalées. Trois des facteurs ci-dessus - DSC, VSC et $CMRO_2$ - sont susceptibles d'affecter le signal BOLD-IRMf, largement utilisé en neurocsiences (Richard B Buxton, 2010), et sont donc de potentiels facteurs confondants dans les études de la cognition dans le vieillissement.

2.1.1.2 Vieillissement et cognition

Le vieillissement normal est associé à des pertes cognitives, mais il reste à établir si le ralentissement du temps de réaction des personnes âgées est simplement le résultat d'un ralentissement général de traitement de l'information (Salthouse, 1996a) ou si certains déficits spécifiques sont touchés de façon disproportionnée dans le vieillissement du cerveau (R. L. West,

1996a). Les fonctions exécutives, dont le centre de contrôle se situe dans le cortex frontal, désignent l'ensemble des processus de contrôle et de surveillance des autres fonctions cognitives, par exemple l'inhibition, la mémoire de travail, la planification, l'attention, l'alternance entre deux tâches, etc. Les partisans de la théorie dite du « vieillissement frontal » lient les déficits des fonctions exécutives à des corrélats bio-physiologiques dans le cortex frontal. En effet, certaines études (compilées par (Drag & Bieliauskas, 2010; R. L. West, 1996a)) ont conclu que la diminution avec l'âge du volume sanguin cérébral (Raz, Rodrigue, & Haacke, 2007), du volume de matière grise (Tisserand et al., 2002) et de l'intégrité de la substance blanche (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009) est plus importante dans le lobe frontal, et ont lié cela à des déficits dans les tâches frontales (exécutives) (Head, Kennedy, Rodrigue, & Raz, 2009). L'hypothèse du vieillissement frontal a néanmoins été remise en question (Greenwood, 2000a; MacLullich et al., 2002a).

Utilisée dans beaucoup de recherches pour étudier le vieillissement cognitif, la tâche de Stroop (Stroop, 1935) exige l'inhibition réussie d'un stimulus interférent au profit d'un autre, ce qui constitue une facette de la fonction exécutive. En règle générale, les sujets sont invités à identifier la couleur d'un mot dont le sens est incongruent (par exemple, "bleu" écrit à l'encre verte). Une abondante littérature a associé le vieillissement avec une augmentation de l'effet d'interférence des stimuli incongurents (Bugg, DeLosh, Davalos, & Davis, 2007; MacLeod, 1991; Mathis, Schunck, Erb, Namer, & Luthringer, 2009; Milham et al., 2002; Prakash et al., 2009; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006; R. West & Alain, 2000). Toutefois, plusieurs autres études (Langenecker, Nielson, & Rao, 2004; Schulte et al., 2009; Uttl & Graf, 1997; Zysset, Schroeter, Neumann, & Yves von Cramon, 2006) et méta-analyses (Ben-David & Schneider, 2009; P Verhaeghen & De Meersman, 1998; Paul Verhaeghen & Cerella, 2002) ont contesté ce point de vue. Ces résultats contradictoires reflètent potentiellement une diversité au niveau des mécanismes du vieillissement cognitif, peut-être liés à des différences physiologiques.

La tâche de Stroop a été étudiée dans différentes expériences de neuro-imagerie utilisant le BOLD-IRMf (compilées par (Derrfuss, Brass, Neumann, & von Cramon, 2005; Laird et al., 2005)), et récemment le BOLD calibré, technique permettant d'estimer le $CMRO_2$ (Gauthier et al., 2013; Goodwin, Vidyasagar, Balanos, Bulte, & Parkes, 2009; Mohtasib et al., 2012). Des différences liées à l'âge ont été mesurées dans différentes régions corticales, y compris le cortex préfrontal, les personnes âgées recrutant des régions supplémentaires liées à l'attention (Milham

et al., 2002; Schulte et al., 2009; Zysset et al., 2006) et montrant des régions d'activation bilatérales et plus diffuses (Mathis et al., 2009) ainsi qu'avec des réponses d'amplitude supérieure (Langenecker et al., 2004; Mathis et al., 2009; Milham et al., 2002; Zysset et al., 2006). Cependant, tous ces résultats doivent être interprétés avec prudence en raison des limitations de l'imagerie pour comparer des groupes dont la physiologie de base est suceptible de différer, tel que démontré dans (Gauthier et al., 2013).

2.1.1.3 Corrélats vasculaires de la cognition dans le vieillissement

Des corrélats vasculaires des troubles cognitifs et des démences sont connus depuis des décennies (Dickstein et al., 2010; Nagai, Hoshide, & Kario, 2010). Chez les adultes en bonne santé de 65 à 75 ans, une étude longitudinale (Mozolic, Hayasaka, & Laurienti, 2010a) a établi un lien entre une augmentation du DSC_0 dans le cortex préfrontal, malgré un volume de matière grise constant, et une amélioration des performances cognitives. (Heo et al., 2010a) ont mesuré une corrélation entre la mémoire et le DSC_0 dans l'hippocampe chez les personnes âgées, soulignant également les corrélats vasculaires de la cognition chez les adultes âgés et l'importance du DSC_0 comme paramètre à mesurer.

Le débit sanguin a été étudié en réponse à des tâches cognitives, mais des études combinant les mesures de BOLD et de débit durant l'activation fonctionnelle chez les personnes âgées ont obtenu des résultats contradictoires en utilisant des tâches et des régions du cerveau différentes. (Ances et al., 2009b), en utilisant l'IRMf calibrée, ont observé une réduction de l'amplitude du BOLD, mais aucun changement dans le nombre de voxels activés ni dans la variation en pourcentage du débit et du $CMRO_2$, en réponse à une stimulation visuelle, dans le groupe âgé. En revanche, (Restom et al., 2007) n'ont trouvé aucune différence liée à l'âge dans l'amplitude du BOLD, mais une hausse du pourcentage de changement de débit en réponse à une tâche de mémoire, compatible avec une augmentation de la réponse $CMRO_2$ avec l'âge. Récemment, Mohtasib et al. ont mesuré une réponse BOLD accrue avec une réponse inchangée en débit à une tâche de Stroop, interprétées comme une diminution du métabolisme et de l'activité neuronale avec le vieillissement (Mohtasib et al., 2012). De ces contradictions flagrantes, émerge l'hypothèse que d'autres facteurs doivent être pris en compte dans les études de vieillissement. La relation apparente de la cognition avec le DSC_0 suggère que la physiologie vasculaire est un facteur clé.

2.1.1.4 Relation entre la santé cardiovasculaire et la cognition chez les personnes âgées

Chez les adultes âgés en bonne santé, certaines études longitudinales (Dustman et al., 1984; Kramer et al., 1999) ainsi que des méta-analyses (S. Colcombe & Kramer, 2003) ont conclu que la santé cardiorespiratoire est associée à de meilleures performances dans les processus de contrôle exécutif (voir (Erickson & Kramer, 2009) pour une courte revue). Cependant, ces conclusions sont remises en cause par d'autres méta-analyses qui, en dépit d'une association significative entre la condition physique et les performances cognitives, n'ont trouvé aucun effet dose-réponse (Etnier, Nowell, Landers, & Sibley, 2006) ou une majorité de comparaisons non significatives (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; van Uffelen, Chin A Paw, Hopman-Rock, & van Mechelen, 2008), concluant que les données actuellement disponibles ne peuvent pas soutenir le rôle direct de la condition physique comme prédicteur de la performance cognitive. Suivant la même tendance, certaines études longitudinales (Madden, Blumenthal, Allen, & Emery, 1989) n'ont pas permis de détecter des effets bénéfiques de l'entraînement cardiovasculaire sur la cognition. L'exercice est aussi connu pour avoir des effets systémiques bénéfiques sur la fonction vasculaire, par exemple en améliorant la fonction endothéliale (Di Francescomarino, Sciartilli, Di Valerio, Di Baldassarre, & Gallina, 2009; Joyner & Green, 2009) et en réduisant plusieurs facteurs de risque périphériques associés au syndrome métabolique et à l'inflammation, eux-mêmes associés à un déclin cognitif (Cotman, Berchtold, & Christie, 2007).

Les corrélats morphologiques et vasculaires de l'effet potentiel de la forme physique sur la cognition ont été étudiés chez l'Homme. Des études transversales en IRM ont associé mise en forme avec la conservation du volume de la matière grise dans des régions du cerveau, y compris le cortex préfrontal (S. J. Colcombe et al., 2003; B. A. Gordon et al., 2008), ainsi que le volume de la substance blanche (S. J. Colcombe et al., 2003) et l'anisotropie fractionnelle (Marks et al., 2007). Des études d'intervention ont confirmé cette relation, montrant des augmentations de volume de la matière grise et blanche dans des régions frontales spécifiques (S. J. Colcombe et al., 2006), ainsi que du DSC et de la connectivité dans l'hippocampe (Burdette et al., 2010). Une augmentation de la vitesse du débit dans l'artère cérébrale moyenne a également été mesurée chez les personnes ayant un VO_2max plus élevé (un indice de la condition cardiorespiratoire) (Ainslie et al., 2008). Un mode de vie actif a également été associé à une amélioration de l'autorégulation cérébrale et une protection contre l'hypoperfusion (Formes, Zhang, Tierney, Schaller, & Shi,

2009). Dans une autre étude, le VO_2max était corrélé avec la réactivité vasculaire cérébrale chez les personnes âgées, mais pas chez les jeunes (Barnes, Taylor, Kluck, Johnson, & Joyner, 2013). Des changements dans l'activation fonctionnelle en réponse aux tâches cognitives ont également été étudiés, trouvant que la bonne forme physique était associée à une diminution des activations dans certaines régions activées avant l'intervention (Lustig, Shah, Seidler, & Reuter-Lorenz, 2009). Chez les primates non-humains femelles, une intervention de cinq mois d'exercice a augmenté le volume vasculaire dans le cortex moteur ainsi que les performances cognitives (Rhyu et al., 2010).

2.1.1.5 Vieillissement et connectivité fonctionnelle à l'état de repos

La connectivité fonctionnelle des réseaux au repos (voir section 3.1.1) a également été un sujet de grand intérêt pour la littérature récente en neurosciences, y compris les études du vieillissement. Dans (Andrews-Hanna et al., 2007), la connectivité fonctionnelle du BOLD semble diminuer dans le réseau du mode par défaut (MD). Dans une étude basée sur le débit sanguin (Y Hao et al., 2011), la comparaison des cartes de débit sanguin au repos des jeunes et des âgés a mis en évidence certains voxels dont la corrélation était renforcée, et d'autres affaiblie, avec le cortex cingulaire postérieur, qui fait partie du réseau MD. Récemment, (Voss et al., 2010) ont étudié les effets d'une intervention d'entraînement cardiorespiratoire sur la connectivité fonctionnelle du BOLD dans 3 réseaux au repos chez les adultes âgés en bonne santé. Ils ont constaté que si la connectivité diminuait avec l'âge, l'exercice augmentait la corrélation dans plusieurs régions des réseaux MD et Frontal exécutif, et ont associé cet effet avec l'amélioration de la performance cognitive dans des tâches de contrôle exécutif.

2.1.2 Modèles animaux du vieillissement cérébral

Même chez l'animal, l'effet de l'âge sur la dynamique de la microcirculation cérébrale n'est pas bien documenté, puisque la mesure de débit dans les vaisseaux sous-surfaciques nécessite des expériences *in vivo* invasives, souvent terminales. Comme alternative, des études post-mortem ont souvent été utilisées pour faire la lumière sur les modifications structurelles de la microvascularisation avec le vieillissement.

2.1.2.1 Changements morphologiques

Plusieurs études des changements morphologiques microvasculaires avec le vieillissement et la maladie ont été publiées (Brown & Thore, 2011; Farkas & Luiten, 2001; Kalaria, 1996; Riddle, Sonntag, & Lichtenwalner, 2003), se concentrant à la fois sur les capillaires et les petits vaisseaux sous-surfaciques (artérioles et veinules). Les changements du diamètre et de la densité des capillaires observés dans ces études pourraient affecter directement la perfusion des tissus avec l'âge. Fait intéressant, plusieurs études rapportent une augmentation du diamètre capillaire avec le vieillissement chez l'homme (Bell & Ball, 1981; Hicks, Rolsten, Brizzee, & Samorajski, 1983; Hunziker, Abdel'Al, & Schulz, 1979) et le rat (Jucker, Bättig, & Meier-Ruge, 1990), bien que cela soit contesté et probablement variable selon la région cérébrale (Hicks et al., 1983; Meier-Ruge, Hunziker, Schulz, Tobler, & Schweizer, 1980). Des « courts-circuits » artério-veineux ont également été observés chez les animaux âgés (Mooradian & McCuskey, 1992). D'autres changements liés à l'âge incluent une diminution de la surface vasculaire (Hunziker et al., 1979) et de la longueur par unité de volume (Brown & Thore, 2011). Certains auteurs rapportent une diminution de la plasticité microvasculaire et de l'angiogenèse (Sonntag, Eckman, Ingraham, & Riddle, 2007). Bien que contredisant certains résultats initiaux (compilés dans (Kalaria, 1996; Riddle et al., 2003)), les études les plus récentes s'accordent sur une diminution liée à l'âge dans la densité capillaire (Ambrose, 2012; Brown & Thore, 2011). Des études réalisées il y a quelques décennies, examinées par (Farkas & Luiten, 2001; Kalaria, 1996; Riddle et al., 2003), associent aussi le vieillissement avec des changements dans l'épaisseur et la composition de la membrane basale des capillaires, de l'endothélium et des péricytes, semblables à ceux observés dans les artérioles. L'épaississement de la membrane basale, les dépôts de collagène périvasculaires et la dégénérescence des péricytes pourraient affecter la rigidité de la paroi capillaire.

2.1.2.2 Dynamique *in vivo*

Dans les grandes artères, des changements de contenu en élastine et collagène (Fritze et al., 2012) au cours de la vie modifient la rigidité de la paroi et le diamètre, conduisant à une augmentation du stress et de la pulsatilité du débit sanguin (Hashimoto & Ito, 2009). À cause de l'augmentation de la pulsatilité, la microcirculation peut être menacée, en particulier dans les organes à haut débit, tels que le cerveau (Riddle et al., 2003). Bien que régulé par les artères, il a été montré

récemment que le débit est pulsatile dans tous les calibres des vaisseaux cérébraux (des artères aux veinules, y compris les capillaires) (Santisakultarm et al., 2012).

Les mesures dynamiques *in vivo* de débit capillaire dans le vieillissement sont plutôt rares dans la littérature. Dans les artérioles de la pie-mère du rat, une étude antérieure (Hajdu, Heistad, Siems, & Baumbach, 1990) a montré une diminution de diamètre, la perte de composants élastiques et une diminution de la distensibilité. En revanche, une étude récente (Bolduc et al., 2011) a mesuré une diminution de la rigidité des artères cérébrales de souris athérosclérotiques *ex vivo*, malgré des artères carotides plus rigides, interprétée comme reflétant des altérations de la fonction endothéliale. Une étude a révélé une augmentation de la vitesse et du débit de 42% et 52% respectivement dans les capillaires du muscle de rats âgés (Russell, Kindig, Behnke, Poole, & Musch, 2003), tandis que la fraction capillaires perfusés, la tortuosité et la ramification ainsi que l'hématocrite capillaire n'étaient pas modifiés.

2.2 Couplage neurovasculaire et réponse hémodynamique

Afin d'étudier le vieillissement dans cette thèse, diverses techniques d'imagerie sont utilisées. Tel que mentionné dans l'introduction, chez l'humain, les techniques les plus répandues de mesure de la réponse neuronale à un stimulus sont en fait des mesures indirectes et se basent sur les corrélats hémodynamiques de l'activité neuronale. Cette section présente la cascade d'événements associés à l'activité cérébrale, relevant des mécanismes du couplage neuro-vasculaire et donnant lieu à la réponse hémodynamique mesurée par ces techniques d'imagerie fonctionnelle.

La propagation d'un influx nerveux nécessite de l'énergie, notamment pour le recyclage des neurotransmetteurs et pour le pompage d'ions contre le gradient électrochimique afin de maintenir le potentiel membranaire à sa valeur de repos (-70 mV). La respiration cellulaire dans les mitochondries peut fournir cette énergie, mais nécessite un apport en glucose et en oxygène. D'autres mécanismes, potentiellement anaérobiques, seraient aussi impliqués dans la production de l'énergie nécessaire à l'activité neurale. Les astrocytes sont des cellules cérébrales de soutien dont la proximité spatiale avec les péricytes et les cellules endothéliales de la paroi des capillaires suggère un rôle dans le contrôle du débit sanguin (Fig. 2-1) (Girouard & Iadecola, 2006).

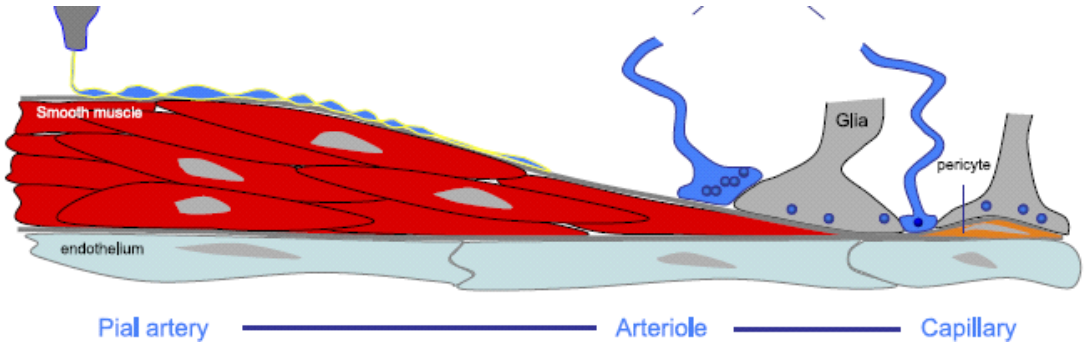

Figure 2-1: Schéma de la paroi d'un vaisseau sanguin cérébral. Les artérioles sont entourées de muscle lisse innervé permettant le contrôle actif du diamètre et donc du débit sanguin. Les parois des capillaires, dépourvues de muscle lisse, contiennent toutefois des péricytes contractiles et des cellules endothéliales qui émettent des agents vasoactifs. Ces cellules sont en contact étroit avec les astrocytes (cellules gliales) ainsi que des projections neuronales. Tiré de (Girouard & Iadecola, 2006).

L'augmentation du débit sanguin cérébral en réponse à un stimulus a été observée depuis plus d'un siècle (Roy & Sherrington, 1890). Le couplage entre activité neurale et changement de débit semble relever d'un système d'interactions complexes et est loin d'être systématiquement linéaire. Chaque étape du couplage neuro-vasculaire, dont l'implication des astrocytes, le lien des neurones au débit sanguin, et du débit au volume, demeure un terrain actif de recherche depuis la dernière quinzaine d'années.

En effet, les mécanismes de l'augmentation du débit ne sont toujours pas connus et résultent de divers facteurs agissant à différents niveaux. Deux grandes hypothèses ont été formulées (Rossier, 2009), qui ne sont pas nécessairement mutuellement exclusives. L'hypothèse métabolique propose un lien de cause à effet entre les besoins énergétiques des cellules et le débit sanguin, peut-être véhiculé par l'accumulation de métabolites vasoactifs, par mécanisme de rétroaction. L'hypothèse neurogénique soutient que le signalement synaptique d'agents vasoactifs émis par divers types de cellules nerveuses régule la dilatation et la constriction des vaisseaux qui contrôlent le débit local. Des données récentes continuent de supporter l'hypothèse métabolique (G. R. J. Gordon, Choi, Rungta, Ellis-Davies, & MacVicar, 2008) comme l'hypothèse neurogénique (Devor et al., 2008; Sirotin & Das, 2009). Des travaux de modélisation ont aussi montré des résultats en faveur d'une dilatation active des vaisseaux sanguins plutôt que d'une redistribution passive du débit sanguin entre les vaisseaux (David A Boas, Jones, Devor,

Huppert, & Dale, 2008). La dilatation de vaisseaux sanguins cérébraux individuels a pu récemment être observée directement (Devor et al., 2008; Kleinfeld, Mitra, Helmchen, & Denk, 1998) grâce à des techniques de microscopie *in vivo* telle que la microscopie biphotonique utilisée dans cette thèse. La distribution spatiale de la dilatation vasculaire en réponse à un stimulus a aussi été étudiée (Lindvere et al., 2013). La réponse biphasique observée dans (Devor et al., 2008) suggère que les réponses de constriction et dilatation sont le résultat d'un équilibre entre les effets antagonistes de différents agents vasoactifs. La diversité des observations obtenues via l'ensemble des expériences menées au fil des années permet de conclure que le couplage neurovasculaire relève de l'action complémentaire de multiples mécanismes médiés par des agents vasoactifs (ions, métabolites et projections neuronales) issus de différents types de cellules et agissant à différentes échelles sur les vaisseaux sanguins cérébraux (Girouard & Iadecola, 2006).

Bien que toute la production d'énergie ne soit pas nécessairement aérobique, le taux de consommation d'oxygène ($CMRO_2$ de l'anglais *cerebral metabolic rate of oxygen*) est un autre paramètre d'intérêt de la réponse hémodynamique, puisque l'oxygénation de l'hémoglobine influence à la fois ses propriétés magnétiques et optiques, exploitées respectivement par l'IRM et l'imagerie optique. Bien qu'il influence le signal BOLD, le $CMRO_2$ ne peut être mesuré directement en IRMf, ce qui en fait un paramètre plus épineux. Des modèles utilisant l'imagerie optique (D A Boas et al., 2003; Jones, Berwick, Johnston, & Mayhew, 2001) ou alors une calibration du signal BOLD basée sur la mesure simultanée de l'imagerie optique (Huppert, Allen, Diamond, & Boas, 2009; Huppert, Diamond, & Boas, 2008), ou du débit sous manipulations de la pression artérielle d'oxygène (T. L. Davis et al., 1998; Gauthier & Hoge, 2012; Hoge et al., 1999a), ont été proposés pour estimer le $CMRO_2$.

L'augmentation du volume sanguin cérébral (VSC), faisant suite à l'augmentation du débit, joue aussi un rôle dans la réponse hémodynamique en augmentant la concentration de sang et donc d'hémoglobine totale dans le tissu. La dynamique temporelle des changements de VSC a été étudiée (Jones et al., 2001) et modélisée (Mandeville et al., 1999), notamment pour son rôle possible dans la forme de la réponse BOLD, qui montre typiquement une diminution sous la valeur initiale avant le retour à la valeur de base (appelé *undershoot* dans la litérature) (Jean J Chen & Pike, 2009).

Si on considère que l'hématocrite demeure constante en réponse à l'activation - hypothèse typiquement acceptée (D A Boas et al., 2003; Hoge et al., 2005; Jones et al., 2001), l'augmentation du volume sanguin se reflète directement dans l'augmentation de la concentration locale d'hémoglobine totale, HbT. Le rapport entre la concentration d'hémoglobine oxygénée (HbO) et désoxygénée (HbR) est modifié en fonction de l'interaction du DSC et du $CMRO_2$, avec au résultat l'augmentation de la concentration d'HbO et la diminution de celle d'HbR (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006). Une réponse hémodynamique typique, mesurée chez des sujets humains normaux, en imagerie optique diffuse (IOD), en BOLD et en ASL, est montrée à la figure 2-2.

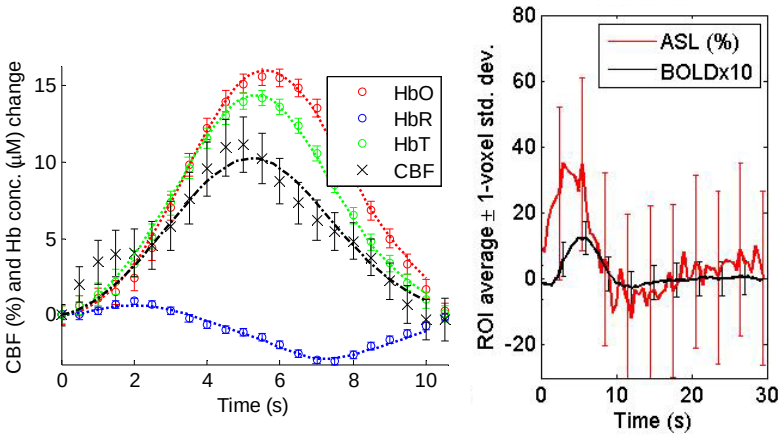

Figure 2-2: Réponse hémodynamique mesurée via différentes modalités. Gauche : imagerie optique diffuse (pour HbO, HbR et HbT) ainsi que spectroscopie de corrélation diffuse (pour le débit sanguin cérébral (ici en anglais CBF)); reproduit de (Michele Desjardins et al., 2009). Droite : imagerie par résonance magnétique mesurant le débit (ASL) et le BOLD. Toutes ces courbes ont été mesurées en réponse à une tâche de mouvement de doigts et moyennées sur plusieurs dizaines de répétitions. Les barres d'erreur représentent l'erreur standard (gauche) et l'écart-type (droite).

Les résultats de la littérature présents dans cette section ont guidé l'établissement des objectifs et hypothèses de cette thèse. Étant donné la controverse entourant les effets possibles de l'exercice sur la cognition chez les personnes âgées, nous avons voulu mesurer cet effet ainsi qu'investiguer certains de ses mécanismes potentiels via des corrélats vasculaires et hémodynamiques dans le cerveau. Il s'agit des travaux présentés dans le second article (chapitre 5). Nous avons aussi voulu expliquer les changements macroscopiques mesurés chez l'humain en fonction des paramètres

microscopiques de la circulation sanguine en utilisant la microscopie dans un modèle animal *in vivo*, puisque de telles mesures du débit microscopique étaient manquantes dans la littérature actuelle. Le chapitre 4 (premier article) présente ces mesures. Enfin, nous avons voulu faire dans le dernier article (chapitre 6) un premier pas dans la liaison des mesures micro et macroscopiques en mesurant la même réponse hémodynamique à l'hypercapnie en microscopie et en imagerie macroscopique (imagerie optique intrinsèque et BOLD).

CHAPITRE 3 ÉLÉMENTS DE MÉTHODOLOGIE COMPLÉMENTAIRES

Cette section a pour but d'expliquer quelques éléments de méthodologie complémentaires à ceux présentés dans les articles qui forment les prochains chapitres, en particulier sur les techniques d'imagerie cérébrale humaine qui sont utilisées dans l'article 2 (chapitre 5) sans que leurs mécanismes soient détaillés (suivant les conventions de la littérature dans ce domaine), ainsi qu'un bref survol des principes de base des techniques d'imagerie animale employées. La description ne se veut pas exhaustive, d'une part par souci de concision et pour éviter toute répétition avec le contenu des articles; d'autre part, car le sujet de cette thèse n'est pas l'instrumentation mais bien l'application de techniques déjà validées à l'étude du vieillissement.

3.1 Techniques d'imagerie cérébrale humaine

Parmi les paramètres de la réponse hémodynamique, plusieurs peuvent être mesurés de façon plus ou moins directe. Cette thèse fait usage de méthodes de deux familles principales: l'imagerie par résonance magnétique (IRM) et l'imagerie optique (IO). Certaines techniques d'imagerie ne permettent que de mesurer des changements par rapport à un état de référence : l'imagerie fonctionnelle repose généralement sur le principe de comparer un état « activé », en réponse à un stimulus ou une tâche, avec un état de base (de repos). L'IRM fonctionnelle (IRMf) et l'IO diffuse en continu (IOD) en sont des exemples. Par ailleurs, certaines techniques permettent de quantifier un paramètre d'intérêt physiologique dans un état donné, en termes absolus, sans besoin de comparer deux états. C'est le cas, par exemple, de la spectroscopie résolue en temps de vol (SRT), une technique optique, ou de l'IRMf-ASL.

3.1.1 Imagerie par résonance magnétique fonctionnelle (IRMf)

Chez l'humain, l'activité électrique des neurones peut être mesurée à la surface du scalp par électroencéphalographie (EEG) et par magnétoencéphalographie (MEG). Toutefois, ces techniques offrent une résolution spatiale limitée, surtout en profondeur dans le cerveau. C'est dans cette perspective que l'IRMf-BOLD (Ogawa, Lee, Kay, & Tank, 1990) s'est imposée comme technique par excellence pour cartographier l'activité cérébrale avec un champ de vue couvrant tout le cerveau et une résolution spatiale de l'ordre du mm^3.

L'IRM est bien connue, mais le lecteur novice peut trouver une introduction très accessible dans (Kastler, Vetter, Patay, & Germain, P, 2000) et plus poussée, quoique toujours pédagogique, sur l'IRM fonctionnelle dans (Richard B. Buxton, 2002a). Selon l'interprétation classique[2], le signal mesuré avec une séquence d'écho de gradient, comme celles utilisées ici, est un voltage induit dans une antenne par le vecteur de magnétisation en mouvement dans le plan transversal par rapport au champ magnétique principal. Ce vecteur de magnétisation peut être vu comme une addition constructive des vecteurs de magnétisation individuels qui sont en phase. Ainsi, l'environnement des spins, en interagissant avec ceux-ci, engendre des déphasages qui modifient la grandeur du vecteur de magnétisation résultant, donc du signal IRM. La magnétisation résultante, et donc le signal IRM, diminue au fur et à mesure que s'accumulent des déphasages; dans une séquence d'écho de gradient, cette relaxation suit une exponentielle avec une constante de temps T_2*.

L'hémoglobine désoxygénée (HbR), paramagnétique, modifie l'environnement des spins et donc leurs déphasage, ce qui a pour effet de modifier T_2*. C'est cet effet, observé en 1990 par Ogawa (Ogawa et al., 1990), qui est à l'origine du signal BOLD (*blood oxygenation level dependent*) qui a érigé l'édifice de la neuroimagerie fonctionnelle depuis. Lors d'une réponse hémodynamique à un stimulus, la diminution de la concentration d'HbR a pour effet d'augmenter T_2* dans l'environnement de la région sollicitée, ce qui implique un signal BOLD plus élevé (Ogawa et al., 1992). Le mécanisme de génération du signal BOLD dépend de beaucoup de facteurs, dont l'oxygénation de base des tissus, les paramètres de la séquences IRM, la géométrie de l'arbre vasculaire, et a été modélisé (Boxerman et al., 1995; R B Buxton, Wong, & Frank, 1998; Richard B Buxton, Uludağ, Dubowitz, & Liu, 2004). Des signaux BOLD négatifs (diminution par rapport à la valeur de référence en réponse à certains stimuli) ont été souvent observés, bien que leur

[2] L'interprétation classique des principes de l'IRM permet de comprendre et de modéliser tous les phénomènes en cause à toute fin pratique. Toutefois, en réalité, la résonance magnétique est un phénomène quantique relevant de l'interaction des moments magnétiques des noyaux de spins demi-entiers dans un champ magnétique. La magnétisation résultante provient de la distribution inégale des spins entre les états de basse et de haute énergie, que permettent de manipuler les impulsions radiofréquences en fournissant de l'énergie, absorbée par les spins qui s'élèvent alors de niveau d'énergie.

origine demeure partiellement incomprise (Devor et al., 2007; Shmuel, Augath, Oeltermann, & Logothetis, 2006).

Les séquences d'IRM par marquage des spins artériels (ASL de l'anglais *arterial spin labeling*) se basent sur un principe de soustraction. En effet, une image sur deux est acquise environ 1,5 à 2 secondes après l'envoi d'un pulse de 180 degrés visant à inverser complètement la magnétisation des spins dans une région en amont de la région imagée. Ainsi, lors de l'acquisition de l'image post-marquage, les spins qui ont voyagé, via la circulation sanguine, de la région de marquage jusqu'à la région imagée auront un signal presque nul. Une image contrôle s'acquiert en appliquant le pulse de marquage à une région en aval de la région imagée, qui n'aura donc pas d'influence sur l'image. En soustrayant l'image marquée de l'image contrôle, on obtient une image proportionnelle à la perfusion (voir Figure 3-1). Plusieurs paires consécutives d'images, en alternant image contrôle et image marquée, peuvent être acquises et soustraites deux à deux afin de générer un décours temporel du débit sanguin. En modélisant adéquatement le signal, on peut calibrer le images obtenues afin d'obtenir une quantification du signal en unités de mL/min/100g (Wang et al., 2003a).

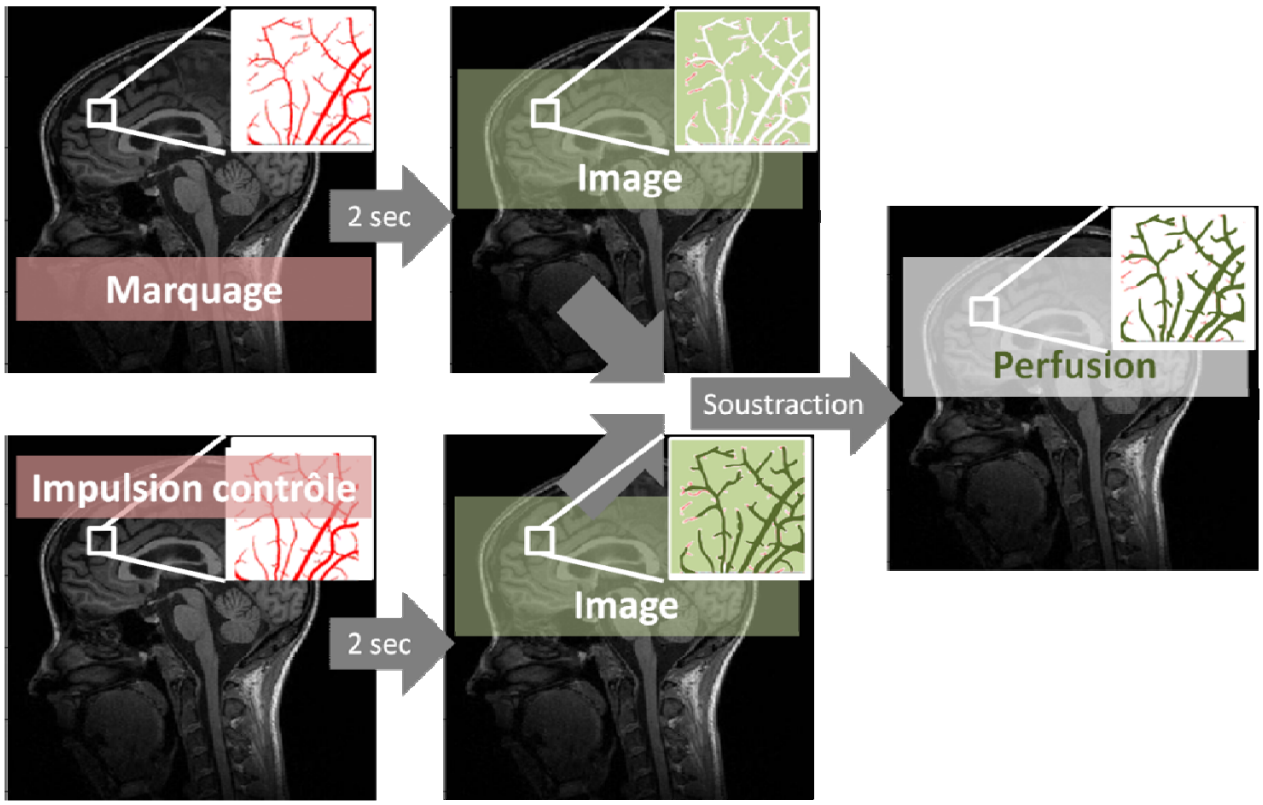

Figure 3-1: Illustration du principe de l'IRM-ASL. L'image contrôle (ligne du bas) est soustraite de l'image marquée (ligne du haut) pour générer une image proportionnelle à la perfusion (à droite).

Traditionnellement, l'imagerie fonctionnelle a été utilisée pour imager l'activité cérébrale en réponse à un stimulus spécifique. Toutefois, il y a une décennie, une nouvelle tendance a émergé, celle de l'étude de l'activité cérébrale au repos, ou spontanée soit en l'absence de stimulus extérieur contrôlé. L'IRM au repos (B. B. Biswal, Van Kylen, & Hyde, 1997; Fox & Raichle, 2007) est ainsi devenue un champ de recherche suscitant beaucoup d'intérêt. Des fluctuations spontanées de basse fréquence (<0.1 Hz) du signal BOLD montrant des corrélations à longue distance entre diverses régions ont été observées, d'abord dans le cortex sensorimoteur bilatéral (B. Biswal, Yetkin, Haughton, & Hyde, 1995) puis dans d'autres régions de tout le cerveau. Ces observations suggérant l'échange d'information entre différentes régions, les fluctuations ont été associées à la connectivité fonctionnelle entre des régions du cerveau considérées comme formant des réseaux aux repos. Certains de ces réseaux ont été mesurés de façon reproductible chez plusieurs sujets humains (Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Perlbarg et al., 2008). Parmi eux, on note le réseau dit « du mode par défaut » (Greicius, Krasnow, Reiss, & Menon, 2003), qui est caractérisé par le fait que son activité diminue lorsque le cerveau est soumis à une tâche ou à un stimulus spécifique. Plusieurs études ont démontré des changements dans le réseau du mode par défaut avec diverses pathologies et conditions, notamment avec le vieillissement (Andrews-Hanna et al., 2007; Y Hao et al., 2011).

3.1.2 Imagerie optique diffuse

L'imagerie optique repose sur la propagation de la lumière dans les tissus. La spectroscopie proche-infrarouge (SPIR) est basée sur l'observation que, dans la plage de longueurs d'onde de 600 à 900 nm du spectre électromagnétique (dans la fenêtre dite thérapeutique), la lumière se propage dans les tissus avec une atténuation réduite. Le mécanisme de contraste est basé sur le fait que, à ces longueurs d'onde, l'oxy (HbO) et la désoxyhémoglobine (HbR) dominent l'absorption de la lumière dans le cerveau (Fig. 3-2A). D'autres chromophores tels que l'eau, le cytochrome oxydase et les lipides atténuent également la lumière, mais leur contribution à l'absorption est marginale et ne peut être mesurée qu'avec un équipement multispectral sensible.

Comme les deux formes d'hémoglobine ont des spectres d'absorption distincts, en utilisant plus d'une longueur d'onde et en connaissant le spectre pour chaque espèce d'hémoglobine, il est possible de les différencier et donc d'inférer sur le taux d'oxygénation du sang.

Dans la pratique, une configuration typique de SPIR se compose d'un nombre limité de sources en des points discrets sur le cuir chevelu qui injectent la lumière à deux ou plusieurs longueurs d'onde (Fig. 3-2B). Les photons injectés seront absorbés et dispersés et certains vont quitter les tissus après un grand nombre d'événements de diffusion. Des détecteurs positionnés sur le cuir chevelu à des emplacements différents sont ensuite utilisés pour collecter la lumière diffusée hors du cerveau. Les sources et les détecteurs sont appelés « optodes ». Leur distance de séparation et leur configuration spatiale déterminent quelle partie du cerveau est imagée (Fig. 3-2C), car plus la source est éloignée du détecteur, plus profondément pénètre la lumière.

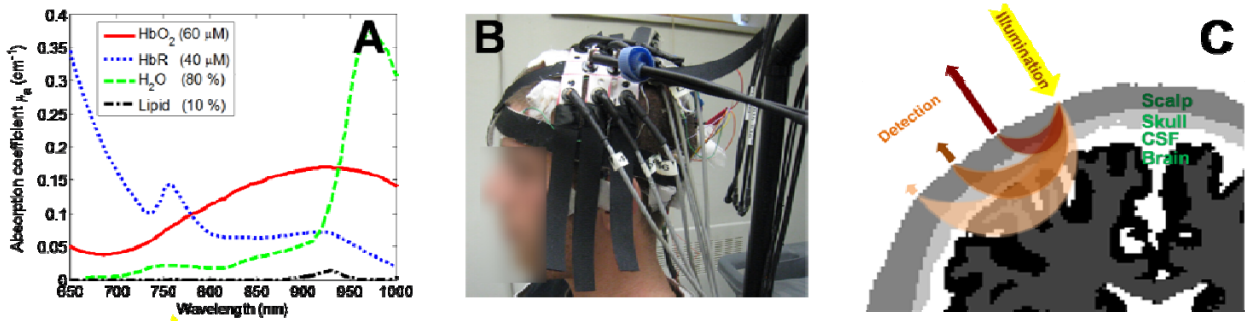

Figure 3-2: A) Spectres d'absorption dans le proche infrarouge pour certains chromophores pertinents en imagerie du cerveau, avec des concentrations supposées entre parenthèses (tracé à partir des données compilées dans (Prahl, 2010)). B) Exemple de configuration d'optodes pour sonder le cortex moteur gauche. Sur cette photo, optodes et électrodes sont combinés pour des enregistrements EEG-IOD simultanés. C) Illustration de la relation entre l'espacement des optodes, la profondeur de pénétration et l'atténuation de la lumière dans un modèle de la tête montrant les différentes couches de tissu. Les plus grandes distances source-détecteur permettent de sonder les tissus profonds mais ont un plus faible rapport signal-sur-bruit. (Reproduit avec permission de (Michele Desjardins, Pouliot, & Lesage, 2012).)

La forme la plus simple et la moins coûteuse de SPIR est l'imagerie optique diffuse (IOD) en continu. Une revue de littérature décrivant les principes ainsi que certaines applications de l'IOD en continu constitue une des publications réalisées durant cette thèse. Le texte n'est pas inclus dans le présent manuscrit, dans l'intérêt de la cohésion et de la concision, mais a été publié

(Michele Desjardins et al., 2012). Dans cette forme d'IOD, la lumière infrarouge est émise et détectée en continu. La loi de Beer-Lambert modifiée (LBLM) (Delpy et al., 1988) est utilisé pour relier l'atténuation de la lumière à des changements dans l'absorption $\Delta\mu_a$:

$$\Phi_\Delta(t,\lambda) = -ln\left(\frac{I(t,\lambda)}{I_0(\lambda)}\right) = -ln\left(\frac{\Phi(t,\lambda)}{\Phi_0(\lambda)}\right) = d \cdot DPF(\lambda) \cdot \Delta\mu_a(t,\lambda), \quad (1)$$

où $I(t,\lambda)$ décrit l'intensité lumineuse mesurée à la longueur d'onde λ, qui, en utilisant des conditions aux limites appropriées, est liée à Φ, la fluence. Les concentrations d'HbO et d'HbR sont calculées à partir des $\Delta\mu_a$ de deux longueurs d'onde, en utilisant les coefficients d'extinction (voir équation (2)). Les facteurs expérimentaux liés à l'efficacité de la détection et au couplage de la lumière avec le milieu s'annulent dans l'équation (1) en normalisant à une mesure de référence, $I_0(\lambda)$. En conséquence, l'IOD en continu ne peut mesurer que des changements de coefficients d'absorption entre deux états et ne peut quantifier les concentrations absolues d'hémoglobine.

À l'opposé, la spectroscopie résolue en temps (SRT) est une technique qui permet de quantifier les valeurs absolues de concentration des chromophores. Dans cette technique, un pulse de lumière très court (de l'ordre de 200-300 ps) est envoyé au cerveau approximant un delta de Dirac (impulsion de lumière). Les photons détectés sont classés selon leur temps de diffusion dans le cerveau (d'où l'appellation « résolue en temps de vol »). L'histogramme des temps de vol des photons constitue une mesure de réflectance, pour laquelle il existe un modèle analytique solution de l'équation de diffusion (Patterson, Chance, & Wilson, 1989). En ajustant ce modèle aux mesures, on estime les paramètres μ_a et μ_s (procédure détaillée dans (Gagnon et al., 2008a)). En utilisant les courbes d'extinction spectrale, l'absorption mesurée (à deux longueurs d'onde différentes λ_1, λ_2) peut être liée à des concentrations d'hémoglobine par

$$\begin{aligned} \mu_a(\lambda_1) &= \varepsilon_{HbO}^{\lambda_1} C_{HbO} + \varepsilon_{HbR}^{\lambda_1} C_{HbR} \\ \mu_a(\lambda_2) &= \varepsilon_{HbO}^{\lambda_2} C_{HbO} + \varepsilon_{HbR}^{\lambda_2} C_{HbR}\,, \end{aligned} \quad (2)$$

où les coefficients d'extinction ε des deux types d'hémoglobine ont été mesurés *in vitro* (Prahl, 2010). Un système SRT peut donc être utilisé pour quantifier les concentrations d'HbO et HbR absolues au repos. Toutefois, puisque la mesure de réflectance nécessite l'intégration des photons sur une période de temps assez longue (300 secondes par exemple), la SRT ne peut pas être

utilisée pour quantifier des changements en imagerie fonctionnelle. En ce sens, IOD et SRT sont complémentaires.

3.1.3 Modèles biophysiques

L'interprétation du signal BOLD est compliquée car ce signal résulte de changements combinés de débit, de volume et d'oxygénation (Buxton, 2010). En particulier pour les études de groupes servant à comparer des populations atypiques, les résultats BOLD doivent être interprétés avec beaucoup de prudence tel que mentionné précédemment. En effet, l'amplitude du signal est influencé à la fois par les paramètres de la séquence IRM et par la physiologie de base, qui définissent l'échelle maximale du signal (un paramètre connu comme "M" dans la littérature) (Davis et al, 1998; Hoge et al, 1999), et par le rapport de couplage entre les réponses métabolique et de perfusion (paramètre "n") (Ances et al., 2008). Non seulement l'interprétation des variations d'amplitude, mais même la détection de régions activées sont tributaires de M et n, puisque certaines valeurs de n peuvent donner lieu à aucune modification du signal BOLD en présence de réponses neuronales et de débit non nulles dans certaines régions (Ances et al., 2008). Des travaux antérieurs ont montré une dépendance de M avec l'âge (Ances et al., 2009). L'influence de la physiologie de base (Cohen et al, 2002; Stefanovic et al, 2006) sur les mesures fonctionnelles suggère la pertinence de mesures de base indépendants (Ances et al, 2009) afin de limiter les facteurs confondants dans l'interprétation des mesures.

Non seulement l'amplitude relative (Ances et al, 2001; Liau et Liu, 2009; Sicard et Duong, 2005; Stefanovic et al, 2006.), mais aussi la dynamique temporelle (Cohen et al, 2002; Liu et al, 2004) de la réponse hémodynamique à l'activation fonctionnelle dépend de la physiologie de base, en particulier du DSC_0 (qu'on peut manipuler expérimentalement en faisant varier la pression sanguine de CO_2 par hypo-ou hypercapnie). Lorsque l'on compare les groupes d'âge qui sont susceptibles de différer en termes de physiologie de base, le biais peut être réduit par la mesure directe de certains des paramètres à l'aide de techniques d'imagerie quantitatives (telles que l'IRMf-ASL et la SRT).

Afin d'interpréter les mesures macroscopiques en termes de paramètres ayant une signification au niveau microscopique, plusieurs approches de modélisation biophysique ont été proposées au cours des dernières quinze années environ. La cytoarchitecture des veines et veinules (Takahashi et al., 1994) cérébrales, qui ne possèdent pas de cellules musculaires lisses contrairement aux

artérioles, suggère que les veines sont compliantes (Schaller, 2004). En conséquence, les vaisseaux veineux cérébraux ont été modélisés comme des tubes souples (Holt, 1941) et, en 1998, un modèle pour l'interprétation des données BOLD a été introduit (Buxton et al., 1998) qui modélise le système vasculaire dans un voxel de tissu cérébral comme un ballonnet gonflé passivement par le débit sanguin issu des capillaires. Des observations expérimentales (Mandeville et al, 1999; Porciuncula et al, 1964) de courbes pression-volume ou débit-volume ont conduit à l'amélioration de modèles biomécaniques de vaisseaux avec « compliance différée » (Mandeville et al, 1999), en utilisant la théorie du Windkessel (Frank, 1899. Sagawa et al, 1990). Au fil des années, plusieurs contributions ont été apportées à la modélisation du couplage neural, métabolique et vasculaire cérébral et son effet sur les signaux fonctionnels mesurables ((Aubert et al, 2001; Behzadi et Liu, 2005; Boas et al, 2008; Buxton et al., 2004; Friston et al, 2000; Huppert et al, 2007; Zheng et Mayhew, 2009; Zheng et al, 2010, 2002) parmi d'autres). Des approches ascendantes (Friston et al, 2000; Huppert et al, 2007) et d'inversion bayésienne (Friston, 2002) ont été proposées pour l'inférence sur les paramètres du modèle à partir de données fonctionnelles. Une de mes contributions comme co-auteure (Dubeau, Desjardins, et al., 2011) présente l'application de modèles biophysiques, dans un cadre bayésien, afin d'interpréter les différences observées dans des mesures d'imagerie optique intrinsèque (voir section 3.2.2) attribuables au vieillissement.

Toutefois, le lien entre les échelles micro et macroscopiques demeure à établir. Dans cette optique, des travaux récents ont modélisé le signal BOLD à partir de mesures microscopiques biphotoniques (voir section 3.2.1) (Gagnon, L., Boas, D. et Lesage, F., travaux non publiés).

3.2 Techniques d'imagerie cérébrale chez les modèles animaux

Les modèles animaux permettent l'utilisation de techniques d'imagerie différentes, notamment des techniques de microscopie invasive dont la profondeur de pénétration limite leur utilisation au petit animal. Avant le développement de l'IRMf-BOLD qui a permis d'importantes avancées dans les études sur le cerveau humain, beaucoup d'études se sont basées sur des techniques d'imagerie optique chez des modèles animaux (Hudetz, 1997).

3.2.1 Imagerie à l'échelle microscopique

La microscopie biphotonique (MBP) est une technique basée sur l'absorption de deux photons de basse énergie qui résulte en la réémission, par fluorescence, d'un seul photon de longueur d'onde différente. Divers agents de contraste permettent de cibler différentes structures, parfois simultanément si les agents ont des spectres d'émission différents.

L'agent de contraste fluorescine-dextran (FITC), injecté dans le sang, permet d'imager le plasma sanguin, parce que ses molécules ne traversent pas les parois des vaisseaux ni celles des cellules sanguines. Les globules rouges apparaissent comme des taches sombres à l'intérieur des capillaires où ils circulent en file indienne. Ainsi, en balayant à répétition un vaisseau le long de son axe, il est possible de suivre le déplacement des globules; c'est le principe utilisé pour mesurer la vitesse du débit sanguin par MBP (Kleinfeld et al., 1998). Par ailleurs, un balayage perpendiculaire au vaisseau permet d'en mesurer le diamètre. Le débit sanguin volumique s'obtient en multipliant la vitesse par l'aire du vaisseau.

Utilisant cette technique, le débit sanguin dans des vaisseaux individuels au repos et en réponse à des stimuli a été étudié (Kleinfeld et al., 1998). Il a été observé que si les artérioles comme les veinules exhibent des augmentations de vitesse et de flux des globules rouges en réponse à l'activation, seules les premières semblent se dilater (Shih et al., 2012).

3.2.2 Imagerie à l'échelle macroscopique

L'IRMf peut aussi être utilisée chez le petit animal, généralement à plus haut champ magnétique offrant un meilleur rapport signal à bruit, comme c'est le cas dans cette thèse où les mesures BOLD-IRMf sur le rat ont été effectuées sur un scanneur ayant un champ magnétique de 7 T. L'imagerie optique intrinsèque (IOI) est une autre technique optique, semblable à l'IOD chez l'humain, mais dans laquelle le cerveau exposé est baigné dans la lumière et la lumière réfléchie est mesurée sur toute la surface d'un champ de vue à l'aide d'une caméra standard (CCD). Le calcul des concentrations d'hémoglobine à partir de l'intensité mesurée s'effectue aussi suivant la loi de Beer-Lambert (voir équations (1) et (2)).

Enfin, la fluxmétrie par granularité laser (FGL) repose sur le principe de la modification du patron d'interférence de la lumière diffusée par des particules en mouvement. Le patron d’interférence généré par la diffusion de lumière laser cohérente sur des particules se nomme

tavelures ou patron de chatoiement (*speckles* en anglais). Lorsque les particules diffusant la lumière se déplacent, le patron d'interférence généré varie dans le temps. Cette variation, intégrée par le temps d'exposition de la caméra mène à une diminution du contraste des tavelures aux endroits où ce mouvement se produit. Ainsi, la vitesse des particules diffusantes (ici les globules du sang) peut être inférée à partir du temps de corrélation du patron, qui en retour peut être relié au contraste spatial mesuré par la caméra (écart-type / intensité). La FGL donne donc une mesure de la vitesse du débit sanguin sur une carte 2D, avec une résolution spatiale de l'ordre de 100 µm et temporelle de 10 ms.

L'IOI et la FGL ont été utilisées pour étudier le vieillissement (Dubeau, Desjardins, et al., 2011) dans un modèle de vieillissement en santé, le rat LOU/c. Dans cette étude, une stimulation somatosensorielle a évoqué une réponse hémodynamique inférieure chez les rats âgés, alors que le $CMRO_2$ estimé semblait inchangé. Une étude de modélisation biophysique basée sur les mêmes données (Dubeau, Ferland, et al., 2011; Dubeau, Desjardins, et al., 2011) suggérait en outre que la compliance des vaisseaux sanguins était modifiée avec l'âge.

Les techniques présentées dans ce chapitre sont utilisées dans les études exposées dans les trois prochains chapitres, afin d'atteindre les trois objectifs de la thèse relatifs aux effets du vieillissement sur le cerveau. Le premier de ces trois articles fait usage de la MBP chez le rat; le second, de la SRT, de l'IRMf (BOLD et ASL) chez l'humain; et le troisième, de l'IOI, de la FGL, de la MBP et du BOLD, cette fois encore chez le rat.

CHAPITRE 4 ARTICLE 1 : AGING-RELATED DIFFERENCES IN CEREBRAL CAPILLARY BLOOD FLOW IN ANESTHETIZED RATS

Cet article présente des mesures en microscopie biphotonique du débit sanguin dans les capillaires de rats jeunes et âgés. Le manuscrit, tel que présenté, a été soumis à la revue Neurobiology of Aging en juillet 2013. Au moment de soumettre cette thèse, l'article est en cours de révision par les auteurs afin de soumettre une nouvelle version.

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4.1 Abstract

Age-related decreases in baseline cerebral blood flow have been measured with various imaging modalities, however, the contribution of capillary flow to this phenomenon remain to elucidate. This study used two-photon laser scanning fluorescence microscopy to measure capillary diameter, red blood cell (RBC) speed and flux in individual capillaries in the sensory-motor cortex of 12 adult (3 months-old) and 12 old (24 months-old) male Long-Evans rats under isoflurane anesthesia. RESULTS: The average (± standard deviation) diameter and speed over 921 capillaries were 6.4 ± 1.4 μm and 1.3 ± 1.1 mm/s respectively. RBC speed and flux were significantly higher, by 48 % and 15 % respectively, in old compared to young animals ($p < 5$ %). The diameter also showed a similar tendency (7% higher, $p = 5.7$ %). Furthermore, capillary

hematocrit and density were significantly lower in the older group ($p < 5\%$), by 32 % and 20 % respectively.

Keywords—two-photon microscopy; cerebral blood flow; aging; capillary; rat; hematocrit

4.2 Introduction

Normal aging is associated with various metabolic and vascular changes, both systemic and organ-specific. In the brain, both structure and function are altered with age. While correlations exist between cognition and perfusion, specific mechanisms of cognitive decline remain unclear and could be manifold, underlying the importance of characterizing changes in blood flow and oxygen delivery with age at the microscopic scale.

Aging-related changes in cerebral blood flow and relation to cognition

Previous studies have measured a regionally specific age-related decrease in baseline cerebral blood flow (CBF_0) in humans, using magnetic resonance imaging (MRI) (Ances et al., 2009a) and positron emission tomography (PET) (Aanerud et al., 2012) among other techniques. A decrease in blood velocity in the large cerebral arteries was also measured using Doppler ultrasonography (Demirkaya, Uluc, Bek, & Vural, 2008). Curiously, in animal models, contradicting results were found regarding age effects on CBF_0. While several studies found region-specific age-related decreases in CBF_0 (Berman, Goldman, & Altman, 1988; Lartaud, Bray-des-Boscs, Chillon, Atkinson, & Capdeville-Atkinson, 1993; Lynch et al., 1999; Ohata, Sundaram, Fredericks, London, & Rapoport, 1981; Rapoport, London, & Takei, 1982), others found no age-related change (Buchweitz-Milton & Weiss, 1987; Salter, Cassone, Wilkerson, & Delp, 1998; Takei, Fredericks, London, & Rapoport, 1983; Tamaki, Nakai, Yokota, & Ogata, 1995) or even increases in CBF_0 (Mitschelen et al., 2009). In both older humans (Bertsch et al., 2009; Heo et al., 2010b; Mozolic, Hayasaka, & Laurienti, 2010b) and rats (Berman et al., 1988; Goldman, Berman, Gershon, Murphy, & Altman, 1987; R. Zhang, Kadar, Sirimanne, MacGibbon, & Guan, 2012), several recent studies observed a relationship between regional CBF_0 and cognitive performance in tasks activating the corresponding regions.

Effects of aging on blood vessels

The effect of age on the dynamics of brain microcirculation is not well documented, since measuring flow in subsurface vessels requires *in vivo* invasive, often terminal, experiments. As an alternative, post-mortem investigations have been used to shed light on structural alterations of microvasculature with aging.

Morphologic changes. Extensive reviews of morphologic microvascular changes with aging and disease have been published (Brown & Thore, 2011; Farkas & Luiten, 2001; Kalaria, 1996; Riddle et al., 2003), focusing on both capillaries and small subsurface vessels (arterioles and venules). Both changes in capillary diameter and density observed in these studies could directly affect tissue perfusion with age. Interestingly, several studies report an increase in capillary diameter with aging in human (Bell & Ball, 1981; Hicks et al., 1983; Hunziker et al., 1979) and rat (Jucker et al., 1990), though this is disputed and probably region-dependent (Hicks et al., 1983; Meier-Ruge et al., 1980). Arterio-venous shunting was also observed in older animals (Mooradian & McCuskey, 1992). Other age-related changes include a decrease in vascular surface area (Hunziker et al., 1979) and length per unit volume (Brown & Thore, 2011). Some authors report a reduction in microvascular plasticity and angiogenesis (Sonntag et al., 2007). Despite contradicting some early results (compiled in (Kalaria, 1996; Riddle et al., 2003)), the most recent studies concur on an age-related decrease in capillary density (Ambrose, 2012; Brown & Thore, 2011). Early reports reviewed by (Farkas & Luiten, 2001; Kalaria, 1996; Riddle et al., 2003) associated aging with changes in thickness and composition of capillary basement membrane, endothelium and pericytes, similar to those seen in arterioles. Thickening of basement membrane, perivascular collagen deposits and pericytic degeneration might affect capillary wall stiffness.

In vivo dynamics. In large arteries, changes in elastin and collagen content (Fritze et al., 2012) over the course of life are known to modify the wall stiffness and diameter, leading to increased stress and flow pulsatility (Hashimoto & Ito, 2009). As a result of increased pulsatility, microcirculation may be threatened, especially in organs with high flow, such as the brain (Riddle et al., 2003). While regulated by resistance arteries, flow was recently shown to be

pulsatile in all cerebral vessel calibers (arteries through venules, including capillaries) (Santisakultarm et al., 2012).

To our knowledge, *in vivo* dynamic measurements of capillary flow in aging are scarce. In rat pial arterioles, an earlier study (Hajdu et al., 1990) found decreases in diameter, loss of elastic components and decreased distensibility. In contrast, a recent study (Bolduc et al., 2011) measured decreased stiffness in cerebral arteries of atherosclerotic mice *ex vivo*, despite stiffer carotid arteries, believed to reflect alterations in endothelial function. One study found higher speed and flux by 42% and 52% in the muscle of older rats (Russell et al., 2003), while the fraction of perfused capillaries, tortuosity and branching and capillary hematocrit were not changed. Thus, age modulation of the speed and flux of blood, of flow pulsatility and of vessel compliance, remains to be elucidated.

Rationale and objectives

The blood-oxygen-level-dependent (BOLD) signal, used in a large number of brain studies, results from a complex interplay between flow, volume and blood oxygenation (Richard B Buxton, 2010), which could be modified with aging (Ances et al., 2009a). Not only the relative amplitude but also the temporal dynamics of the BOLD signal has been found to depend on baseline physiology, in particular CBF_0 (Cohen, Ugurbil, & Kim, 2002). A significant proportion of the BOLD signal is thought to originate from the microvasculature and capillaries (Boxerman et al., 1995; Pathak et al., 2008). Thus, a thorough understanding of the evolution of cerebral perfusion with aging is crucial for interpreting the large body of research conducted on cognition and aging using BOLD. In particular, understanding and quantifying age-related changes at the level of capillaries, where most substance exchanges with brain cells take place under the control of the blood-brain barrier, is required.

Two-photon laser scanning fluorescence microscopy (TPM) was recently applied to study blood flow in individual brain microvessels (Kleinfeld et al., 1998). TPM combines good depth penetration, at least 500 μm in cortex tissue, enough to probe different cortical layers in rodents (DeFelipe, 2011), with good enough lateral resolution (~1 μm with our 20x objective) to study individual capillaries. In this work, we used TPM to measure capillary flow in two groups of rats, young adults and old. The goal was to investigate the effect of aging on flow dynamics in cortical

capillaries. Specific parameters were targeted in order to characterize microvascular CBF_0: red blood cell velocity, internal capillary diameter and local hematocrit. To our knowledge, this study provides the first measurements in cerebral capillaries of living anesthetized older animals, which is crucial for dynamic parameters such as blood flow that cannot be studied *ex vivo*. Furthermore, compared to previous microscopic studies of capillaries, we believe the large number of vessels measured here is unprecedented.

4.3 Methodology

Animal preparation

Twelve adult (11-15 weeks-old: Y) and 12 old (23-25 months-old: O) male Long-Evans rats were used in this study. During their first 22 months of age, old rats were on a slightly calorie-restricted diet (20 g/day, Teklad Global 18% Protein Rodent Diet) and did not exercise. They were housed on a 12-12 hour light-dark cycle, in large cages containing 3 to 4 animals. At 22 months of age, the older rats were transported to the imaging facility and housed in the same conditions as the young ones. Thus, for two to ten weeks preceding the experiment, all animals were housed in individual cages with a 12-12 hour light-dark cycle. All procedures were approved by the animal ethics committee of the research center of the Montreal Heart Institute.

On the day of the experiment, the animal was anesthetized with isoflurane for the whole duration of the experiment (8-15 hours) and then sacrificed. Anesthesia was induced with 2.75% isoflurane in 1.5 L/min pure oxygen and a non-steroidal anti-inflammatory drug (ketoprofen, 5 mg/kg body weight) was injected subcutaneously. Throughout the experiment, the anesthesia level was maintained by adjusting the level of isoflurane between 1.5 and 2% in freely breathed oxygen to effectively suppress the hind paw withdrawal and blinking reflexes. During surgery and data acquisition, the rat's physiological parameters (respiration, heart rate, arterial blood pressure and temperature) were continuously monitored and recorded. Body temperature was maintained at 37 °C with a temperature-controlled heating pad working with feedback (PhysioSuite, Kent Scientific, CT, USA). A breathing sensor and subcutaneous electrodes provided the respiration rate and the ECG. A catheter was inserted in the femoral artery to monitor blood pressure (Millar, TX, USA) and another one was inserted in the femoral vein for

injection of the contrast agent. The animal was positioned on a stereotaxic frame (WPI, FL, USA) fitted with atraumatic ear bars. A section of ~ 5 mm x 5 mm cortex was exposed by removing skull and dura mater over the right sensorimotor cortex (1-5 mm relative to the bregma point, 1-7 mm from the midline on the medial-lateral axis (Shih et al., 2012)). The craniotomy was sealed with a glass cover slip fixed with agarose (1% in artificial CSF (Nimmerjahn & Helmchen, 2012)). Just before imaging, we injected intravenously ~150 mg/kg of fluorescein isothiocyanate–dextran (FITC, molecular weight 70 kDa, Sigma Aldrich, ON, Canada) at a 100 mg/mL concentration in saline. For very long experiments, supplementary doses (~15-25 mg) were added after a few hours.

Two-photon microscopy setup

Measures were made on a custom-built two-photon microscope controlled by a LabVIEW interface (National Instruments, TX, USA). An adjustable-wavelength laser (MaiTai-BB, Newport corporation, CA, USA) output ~2 W through an acousto-optic polarizer used to adjust the gain for depth-dependent excitation intensity. Excitation and detection wavelengths used for FITC were 800 nm and 520 nm, respectively. The light beam was scanned over a region of interest of 800 μm x 800 μm on the sample using galvanometric mirrors. Light was focused on the sample and its reflection collected using a 20x objective (NA = 1), then separated into 4 beams using dichroic mirrors. The first beam was sent to an avalanche photodiode measuring non-fluorescent reflection and was used to localize surface elements on the sample. The other beams were split and filtered to wavelengths of 460, 520 and 593 nm, and measured on three photomultiplier tubes (Hamamatsu Photonics, Japan). The user interface allowed real time display of the recorded images.

Data acquisition

For each animal, an angiogram was first measured as a 3D scan over a 800 μm x 600 μm x 500 μm region scanning the mirror galvanometers on planes of different depths (z), by steps of $\Delta z = 2$ μm. The angiogram was then used to localize capillaries and guide manual positioning of line scans across and along targeted vessels (see Fig. 4-1). Thus, each capillary was scanned both perpendicularly (to measure diameter) and longitudinally (to count red blood cells). These line

scans measured 200 points along a variable-length (~25 μm) line at a rate of 400 kHz (line-rate = 2 kHz), alternating between the perpendicular and longitudinal scans of the same vessel. Line scans were repeated continuously during ~45 s to allow averaging. In each animal, as many capillaries as possible were measured, yielding between 12 and 93 successfully measured capillaries per animal depending on the success of the surgery and the rat's health.

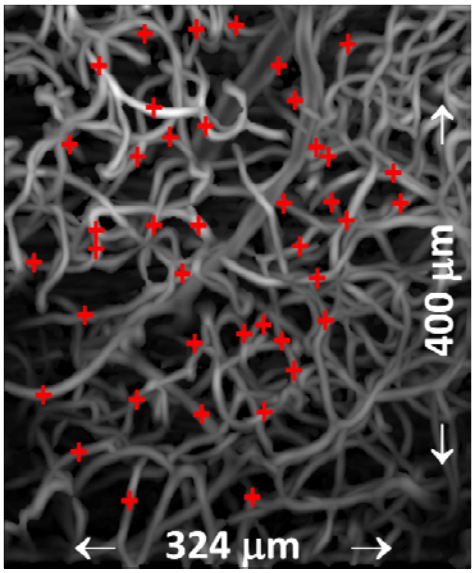

Fig. 4-1. Positioning of line scans on individual capillaries based on an angiogram. A maximum intensity projection of a 3D volumetric scan from one animal is shown with red crosses representing each capillary measured in this region. The 3D scan was filtered to enhance tube structures using Fiji (Schindelin et al., 2012). The image shown here includes the first 300 μm just below large surface vessels, while the 41 capillaries measured were mostly in the first half of this depth.

Data analysis

All analyses were performed in Matlab (MathWorks, MA, USA) using in-house code. Because the contrast agent is contained in blood plasma, red blood cells (RBCs) appear as dark spots inside the capillaries where they flow along a single file. Following the movement of those spots through successive line scans over the same region is the principle for measuring RBC flow (Fig. 4-2) (Kleinfeld et al., 1998).

Vessel diameter: Perpendicular scans clearly show the vessel profile (see Fig. 4-2C), which was fitted to a Gaussian function whose full-width at half-maximum defined the vessel diameter.

RBC speed: The concatenation of successive longitudinal scans in a vessel with moving RBCs yielded a space-time image with diagonal dark streaks, as illustrated in Fig. 4-2D. The angle of the streaks was determined as the angle θ at which the Radon transform of the image had the greatest variations (Santisakultarm et al., 2012). Then, tan θ provided the inverse-slope, $\Delta y/\Delta t$, of the streaks. The velocity in mm/s was finally computed by multiplying the inverse-slope by the size of a pixel in mm and by the acquisition rate in Hz. The sign of the velocity provided the direction of flow relative to that of the scan, and the speed was simply its absolute value. The volumetric flow was the product of the speed by the vessel cross-section ($\pi \cdot (\text{diameter}/2)^2$).

Flux and hematocrit: In capillaries, where the RBCs circulate in a single file, the flux of RBCs is equal to the number of dark streaks in a space-time image (like Fig. 4-2D) divided by the time taken to acquire this image (e.g., 100 ms in this case). The streaks were counted automatically by detecting minima in filtered longitudinal images. Dividing by speed, we obtained a linear RBC density, and dividing again by vessel area, a volumetric density. Multiplying by the volume of a RBC (60 μm^3 (Hawkey, Bennett, Gascoyne, Hart, & Kirkwood, 1991)) we estimated the volume fraction of RBCs in blood, i.e. the hematocrit.

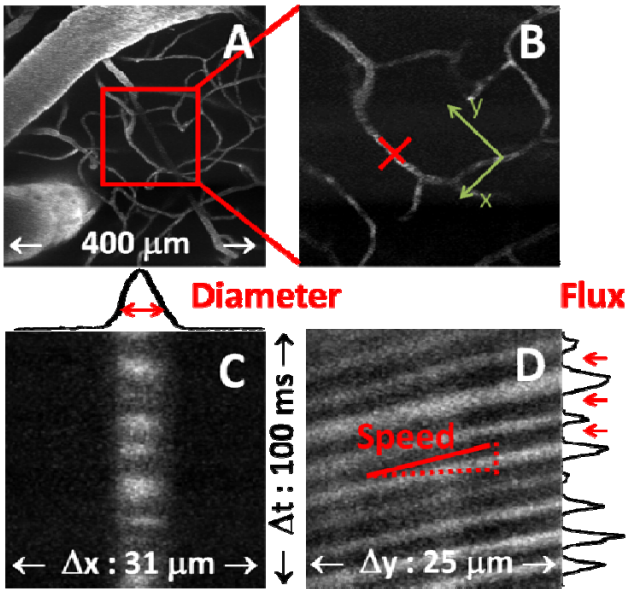

Fig. 4-2. Measurement of red blood cell (RBC) flow using line scans. (A) Maximum intensity projection over 60 μm thickness of one acquired angiogram. (B) Zoom showing position of the perpendicular and longitudinal scans of a capillary. (C) Intensity profile of a scan and 200-scans image for a perpendicular scan, used to measure diameter. (D) Intensity profile and 200-scans image for a longitudinal scan, used to measure RBC flux (number of cells per unit time) and speed. Alternating bright and dark pixels represent the plasma and the RBCs which, as they are moving over time, appear as dark streaks in the position-time image. The slope of those streaks is the inverse of RBC speed. In this example, the diameter was 5.1 um, the flux 80 cells/s (8 cells in a 100 ms image), and the speed 0.17 mm/s.

For perpendicular and longitudinal scans, data was recorded for around 45 s. For each vessel, the median value over the time course was used as a measure for RBC speed, vessel diameter and flux. For each animal, measurements from all capillaries (N = 12-93, mean 38 per animal) were averaged to yield one measure per animal. The number of capillaries measured per animal was not significantly different between the two groups ($p > 30$ %). Data from the two age groups were compared using Student's t-tests for each variable (see Results section).

Angiograms were processed using Fiji (Schindelin et al., 2012) in order to compute capillary density. A median filter (3x3x3 pixels) and a histogram equalization were used to reduce noise and enhance contrast. Tubular like features of diameter between 5-8 μm in the angiograms were then enhanced slice by slice using Fiji's implementation of Sato's filter (Sato et al., 1998). The vascular enhanced volumes were transformed into local thickness maps assigning to every pixel the diameter of the maximal sphere that can fit locally (Hildebrand & Rüegsegger, 1997). The capillary density was defined as the number of pixels with diameter smaller than 10 μm divided by the total volume. Visual quality control was subsequently performed to insure that the algorithms correctly identified capillaries.

4.4 Results

The distributions of diameter, speed and hematocrit, over all capillaries measured in each age group, are shown in Fig. 4-3. Measures were not normally distributed (based on a chi-square test) and were generally more outlier-prone than a normal distribution. The kurtoses of the diameters distribution were 4.4 and 5.2 (3.1 and 2.7 when excluding the 2% highest values) for the young

and old groups respectively, and those of speed were 22.4 and 14.8 (6.2 and 4.2 excluding the 2% highest values); these were not significantly different between the two groups.

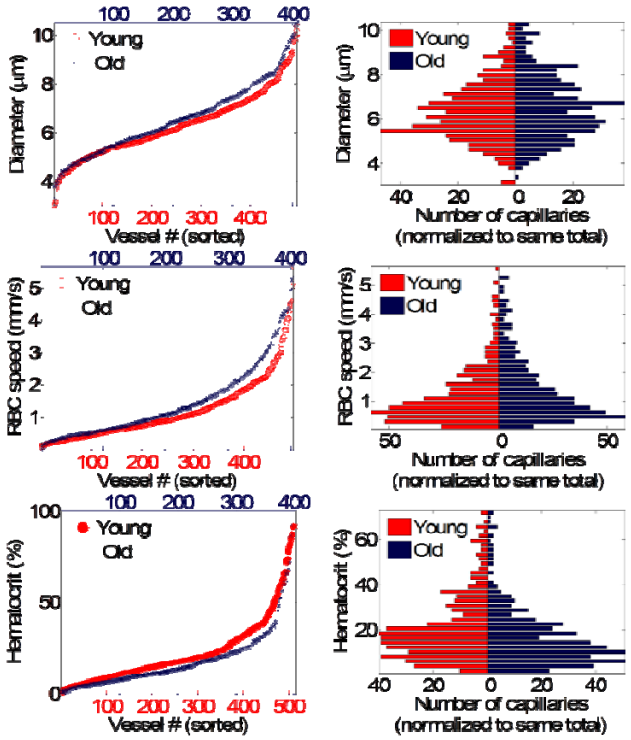

Fig. 4-3. Distribution of data from all capillaries in young and old rats.

The average values over all animals in each age group are shown in Table 4.1. RBC speed, flow and flux were significantly higher in the older group. Diameter was also measured larger in the older rats, but this effect did not reach statistical significance at $\alpha = 5\%$ ($p = 5.7\%$). The hematocrit was significantly lower in the older group. The time fluctuations of the speed (standard deviation over each ~45 second scan) were significantly higher in the older group ($p < 1$ %). The spatial heterogeneity (standard deviation of the mean speed over all capillaries in each animal), was significantly higher in older animals, but there was no difference in the relative heterogeneity (normalised to the mean speed for each animal). Finally, analysis of the angiograms revealed a significant decrease in capillary density in the older animals ($p < 1$ %).

Table 4.1 : Measured flow parameters

Parameter	**Group**		**% Change (Y → O)**
	Young	Old	
Number of capillaries	498	405	
Diameter (μm)	6.2 ± 0.1	6.6 ± 0.2	+7 % [a]
RBC speed (mm/s)	**1.0 ± 0.1**	**1.5 ± 0.2**	**+48 % ***
Capillary flow (pL/s)	**35 ± 5**	**54 ± 6**	**+53 % ***
RBC flux (cells/s)	**95 ± 5**	**110 ± 5**	**+15 % ***
Hematocrit (%)	**31 ± 3**	**21 ± 1**	**-32 % ****
Speed temporal fluctuations (%)	**33 ± 3**	**67 ± 8**	**+104 % ****
Speed spatial heterogeneity (mm/s)	**1.3 ± 0.2**	**1.8 ± 0.2**	**+43 % ***
Relative speed spatial heterogeneity (%)	129 ± 8	122 ± 3	-5 %
Capillary density (% of total volume)	6.8 ± 0.3	5.4 ± 0.3	**-20 %****

Values shown are group mean ± S.E.M.

Star symbol and bold denote statistically significant difference between the two groups
(* : $p < 5$ % ; ** : $p < 1$ %)

a. $p = 5.7$ %

Results presented are based on 903 of the 921 measured capillaries, excluding the 2% with highest speeds and 2% with largest diameters. We excluded the extreme values in order to insure studying strictly capillaries and not precapillary arterioles, based on literature values for capillary diameter and speed. However, statistical comparisons between groups, or group average values presented in table 4.1, did not change when including all measures.

Figure 4-4 illustrates relations between measured variables. The fluctuations of speed did not appear to be correlated with its absolute value (r = -0.18). Diameter and speed were weakly positively correlated (r = 0.27). RBC flux was correlated with speed (r = 0.75) and vessel diameter (r = 0.33). Finally, hematocrit was inversely correlated with diameter (r = -0.61) and speed (r = -0.61). Figure 4-4 indicates that a linear relation is not optimal to describe these correlations.

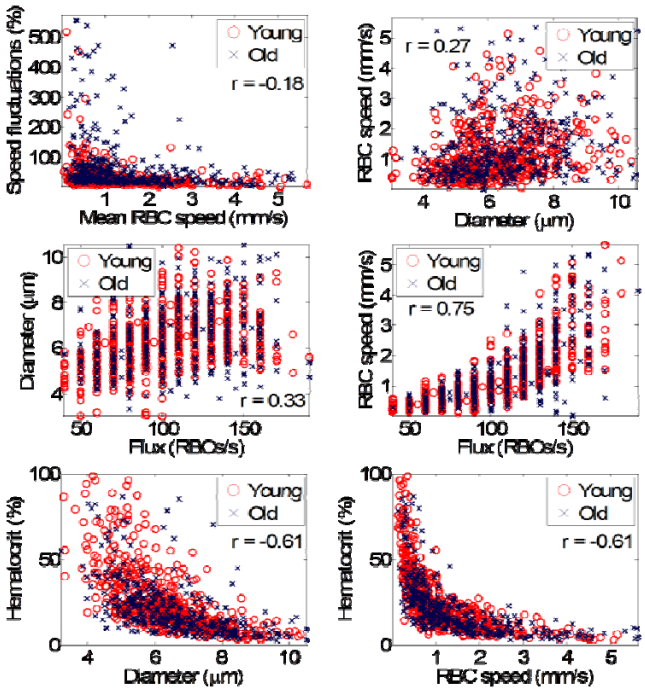

Fig. 4-4. Relations between measured variables across all capillaries.

4.5 Discussion

Relevance and interpretation of results

Mean values of speed, diameter and hematocrit. Literature reports quite discrepant values for RBC speed in capillaries: in the range of 0.1 to 4.2 mm/s, with averages between 0.5 and 2 mm/s (Hudetz, 1997; Kleinfeld et al., 1998; Unekawa et al., 2008, 2010). However, as shown in (Unekawa et al., 2008), some reported values might depend on the measurement technique, and some earlier studies might not have had sufficient frame rates to measure the highest speeds. Our measures from 903 capillaries fall in this range of literature reported values. However, a small fraction (2%) of measures were considerably higher, between 5 and up to 14 mm/s, in both young and old animals. We hypothesize that these values might originate from precapillary arterioles or from arterio-venous shunts, previously observed in older animals (Mooradian & McCuskey, 1992), indistinguishable from regular capillaries during vessel selection. In consequence, we excluded the 2% highest speeds from our analyses to insure that we compared only capillaries. Capillary diameters were reported between approximately 5-7 μm in (Kleinfeld et al., 1998), similar to our values, but higher than an average value of 3.7 μm measured elsewhere with the same technique, TPM (Hutchinson, Stefanovic, Koretsky, & Silva, 2006).

When comparing with literature data, one must be careful about the definition of measures. For example, diameter measured *in vivo* always reflects both vessel structure and tone, since the diameter is regulated (Farkas & Luiten, 2001). In the case of TPM measurement with plasma fluorescence, the lumen diameter was obtained (as opposed to external diameter). In addition, the measured diameter might depend on membrane thickness. Finally, some of the hematocrit values are noticeably high: this is probably due to the fact that hematocrit is derived from combined speed, flux and diameter measurements, as well as assumed RBC volume, leading to larger measurement errors. Nonetheless, our mean (± std) measured hematocrit in individual capillaries, (21 ± 17) %, is very similar to that reported recently in (Santisakultarm et al., 2012), which was (22 ± 19) %.

Relations between variables. Our data showed that speed and diameter were weakly positively correlated. In a literature review on cerebral capillary flow, Hudetz (Hudetz, 1997) reports a

linear relation between speed and diameter, while this relation is not seen in the data from Kleinfeld et al. (Kleinfeld et al., 1998), perhaps because of a small number of measurements. Our data also showed a strong correlation between speed and flux, in concordance with the data in (Kleinfeld et al., 1998). Our hematocrit measurements were inversely correlated with diameter and RBC velocity. Hudetz reported a similar inverse relation between hematocrit and speed following carotid occlusion (Hudetz, 1997). In the recent measures by Santisakultarm et al. (Santisakultarm et al., 2012), hematocrit was weakly inversely correlated with vessel diameter, but not RBC speed.

Age-related changes. We observed larger diameters and higher RBC velocities in the capillaries of older animals. Previous studies have observed age-related diameter increases (Bell & Ball, 1981; Hunziker et al., 1979; Jucker et al., 1990). A possible explanation for such an *in vivo* diameter increase is that changes in endothelium function and innervation, also previously observed, can cause changes in reactivity and vessel tone, which lead to changes in operating diameter. A hypothesis for explaining changes in velocity in the capillaries is that age-related changes in membrane composition and stiffness in arterioles upstream affect the blood flow and speed downstream.

In our data, capillary density decreased by 20% in older rats. In a recent literature review, (Brown & Thore, 2011) report previous studies of capillary density and number in different brain regions. Nine different studies in rats measured age-related decreases in capillary density between 12-33 %, in capillary numbers between 8-43 %, and increases in inter-capillary distances between 6-48%. Thus, our results fall in the middle of the broad range of previous measures in rat brain.

Cerebral blood flow. Many studies have reported *decreases* in global and regional cerebral blood flow with aging at a macroscopic scale. Based on literature from human data (see Introduction), a ~20%, that is 0.5-2 standard deviations, decrease in CBF_0 between young and older adults has been observed. Surprisingly, our data show a 54% *increase* in individual capillary flow in the older group relative to the young group. Volumetric flow in a given brain region (in mL/min/100g brain tissue) depends on individual flow and on the density of vessels. We observed a 20 % decrease in capillary density, which could result in decreased volumetric flow despite higher flow in individual capillaries.

A hypothesis explaining our observed capillary flow increase could be that as flow decreases in arterioles, compensatory mechanisms are developed in capillaries (such as increased diameter) to maintain tissue perfusion. A change in input pressure to the capillary network, caused by changes in arteries and arterioles, would influence capillary flow. For instance, if pressure at the output of cerebral arteries was increased as a result of altered compliance, it might explain a speed increase at the level of capillaries. Larger speed temporal fluctuations in older animals suggest that the pulsatility of flow might be higher and could reflect a change in vessel compliance with aging.

Morphologic changes (in segment lengths, tortuosity and connectivity) which influence resistance and total surface area of the vessel network, could also alter CBF_0. Another possible explanation for our observations is that there is simply no CBF_0 decline in rats in the region studied (S1), as vascular morphometry seems to be region-dependent and potentially species-dependent. Nonetheless, a recent study showed a similar distribution of RBC flow speed across species (rat and mouse) (Unekawa et al., 2010). Future studies measuring CBF_0 are needed to allow comparison of microscopic and macroscopic flows.

Hematocrit. Previous studies found a slight age-related decrease in systemic hematocrit during adulthood, potentially gender-dependent (Cirillo, Laurenzi, Trevisan, & Stamler, 1992; Hiroshi Ujiie, 2012). Our data also showed a decrease in local hematocrit measured in single capillaries, which might differ from systemic hematocrit. Lower hematocrit is associated with lower blood viscosity, which means lower resistance and possibly higher velocity, thus possibly higher CBF_0 (Farkas & Luiten, 2001; Harrison, 1989; Hudetz, 1997), though hematocrit might not explain an observed age-related viscosity change (Ajmani et al., 2000; Oder et al., 1991). Our results are in concordance with this, as older animals had lower hematocrit and higher speed.

Local hematocrit plays a role in the perfusion of tissue with oxygen bound to the RBCs. As oxygen transfer results from unbinding of O_2 molecules from RBC to blood plasma and then diffusion through vessel membrane to parenchyma (Thomas, Lefrak, Irwin, Fritts, & Caldwell, 1974), and diffusion is limited in time by a diffusion constant, higher speed is associated with lower oxygen extraction. This effect has been modeled in biophysical models (R B Buxton & Frank, 1997; Fang et al., 2008). It could be hypothesized that lower hematocrit and higher speed are causes for lower oxygenation in aging, in concordance with previously observed decreases in

cerebral metabolic rate of oxygen consumption ($CMRO_2$) in humans (Leenders et al., 1990a; Pantano et al., 1984; Takada et al., 1992; Yamaguchi et al., 1986). However, microscopic studies directly aimed at metabolism are needed to clarify this issue. Towards this goal, two-photon microscopy allows to simultaneously measure flow and pO_2 (Sakadzić et al., 2010) and can be combined with electrophysiological measurements of neural activity.

Heterogeneity. An interesting observation is the heterogeneity of the speed between capillaries within each animal. The standard deviation of RBC velocity was, on average 1.5 ± 0.2 mm/s (± S.E.M) over animals, that is 125 ± 6 % of mean speed. Speed heterogeneity between capillaries seen in our data is in concordance with previous observations (Hutchinson et al., 2006; Kleinfeld et al., 1998; Pawlik, Rackl, & Bing, 1981; Villringer, Them, Lindauer, Einhäupl, & Dirnagl, 1994). A recent model has been proposed (Jespersen & Østergaard, 2012) which describes the role of capillary transit time heterogeneity in supplying oxygen to the brain. It suggests that higher heterogeneity, especially at shorter transit times (higher speeds), results in lower oxygen delivery to tissue relative to homogeneous transit times across capillaries. This is of particular interest in relation to the present study because aging might cause such alterations. In our data, absolute speed heterogeneity over all vessels was larger in older animals. However, when considering only animals with at least 20 or 30 capillaries measured, considered a minimal number for measuring heterogeneity, the age difference was not significant. The difference was also not significant when considering the heterogeneity (standard deviation) normalized by the mean speed over all capillaries for each animal. Thus animals with higher mean speeds had higher heterogeneity, but our data does not support an age-related difference in speed regulation. Potential changes in heterogeneity with aging might be subtle and a larger sample of animals might be required.

Blood pressure. Biophysical models describe blood pressure (BP) as a determinant of blood flow and volume, thus diameter (David A Boas et al., 2008; Mandeville et al., 1999). Thus, variations of BP over time or between animals could influence our results. We continuously measured systemic arterial BP during all experiments (except for one animal) using a femoral catheter. In most animals, pressure varied throughout the experiment with standard deviation between 1-26 %. These variations and inter-subject differences are possible sources of error, however, we

found no correlation between BP and measured speed (in terms of fluctuations around median) within each animal, except for 2 animals with a weak (significant) inverse correlation. Diameter and BP were also not correlated, except in 1 animal.

Limitations

Some limitations arise from experimental factors. Manual vessel selection in our experiments might have caused a bias towards larger, clearer capillaries. Seventy percent of measured capillaries were situated between 0-100 μm below the larger surface vessels, so that most of our results are from layers I and II of the cortex, with some measurements as deep as layer IV (350 μm) (DeFelipe, 2011).

Isoflurane is known to be a vasodilator, and controlling the level of anesthesia, which might have varied slightly between animals, could also influence measurements and increase variability (Franceschini et al., 2010). Anesthesia is also known to influence neurovascular response and thus potentially flow dynamics, relative to the awake state. In this experiment, the level of anesthesia was controlled based on physiological parameters (blood pressure, cardiac and respiratory rates), but could still be a confounding factor, for example since its effects might not be identical in older animals. Chronic preparations to measure blood flow in awake animals (Shih et al., 2012) may be required to remove anesthesia confounds.

4.6 Conclusion

This study investigated differences in capillary blood flow between young adult and old anesthetized rats. Red blood cell velocity and capillary diameters were measured higher in older animals, meaning that single-capillary flows were higher. However, the density of capillaries was decreased in older animals. Hematocrit was also lower in the older rats. Taken together, these results shed light on changes in perfusion and oxygen delivery to the brain with aging. In the medium term, *in vivo* two-photon microscopy using rapid line scans in individual vessels could help gain insight on the effect of various pathologies on microvascular circulation.

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CHAPITRE 5 ARTICLE 2 : ASSOCIATION OF CARDIOVASCULAR FITNESS WITH COGNITION, CEREBRAL BLOOD FLOW AND OXYGENATION IN AGING

Cet article relate une série de mesures d'imagerie fonctionnelle (IRMf BOLD et ASL), de physiologie de base (DSC_0, HbT_0 et sO_{20}), de cognition (temps de réactions et proportion de bonnes réponses à la tâche Stroop) et de la santé cardiorespiratoire (VO_{2max}) chez des sujets humains jeunes et âgés. Ces résultats permettent d'explorer certains corrélats physiologiques et vascualires de l'effet d'exercice sur la cognition. Le manuscrit a été soumis à la revue NeuroImage le 1er octobre 2013. En date de la soumission de cette thèse, il est en révision afin de resoumettre un texte corrigé en réponse aux corrections demandées par les réviseurs.

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5.1 Abstract

Normal aging has been associated with various changes in the brain, but results regarding cognitive decline and the beneficial effects of cardiovascular exercise still lack consensus. This

study investigated cerebral baseline flow (CBF_0) using arterial spin labelling functional magnetic resonance imaging (ASL fMRI), as well as cerebral oxygenation (SO_{20}) and regional total hemoglobin concentration (HbT_0) using time-resolved spectroscopy, in young (24.4 ± 2.5 years-old) and aged (67.6 ± 2.9 years-old) subjects. Cardiovascular fitness was quantified using a VO_2max test to separate high-fit from low-fit individuals and cognitive performance was assessed from a Stroop task performed during a blood-oxygenation-level-dependent (BOLD) fMRI scan. Older adults had significantly lower total (by 21%), gray matter (18%) and left prefrontal (19%) CBF_0, as well as lower left prefrontal HbT_0 (21%) and SO_{20} (6%). Functional connectivity, measured on resting-state flow, was lower in some frontal regions of the default mode network (DM) for older adults compared to young. The Stroop task interference solicited a left prefrontal region where older lower-fit individuals had higher BOLD activity in response to the Stroop. In aged adults but not in young ones, lower VO_2max was associated with slower reaction times and age-related slowing was significantly more important among low-fit individuals compared to high-fit. SO_{20} was correlated with VO_2max and with cognitive performance in aged adults, while this correlation was not significant for neither CBF_0 nor HbT_0. These results suggest that exercise might have a protective effect against aging-related cognitive decline and that cerebral oxygenation is a significant correlate of this effect.

Keywords - Aging; VO_2max; arterial spin labelling; blood-oxygenation-level-dependent signal; time-resolved spectroscopy; Stroop; resting-state networks; cerebral blood flow.

5.2 Introduction

Unravelling the mechanisms of cerebral aging has been the subject of a large amount of research. Aging has been associated with decreased regional baseline metabolic rate of oxygen ($CMRO_2$) measured by PET (Kalaria, 1996; Marchal et al., 1992), though this finding has been controversial (Bentourkia et al., 2000b; Tumeh et al., 2007b). In humans, regional baseline cerebral blood flow (CBF_0) was found to decrease with increasing age, though not always in a linear fashion, in studies using MRI (Ances et al., 2009b; Asllani et al., 2009b; Biagi et al., 2007b; Parkes, Rashid, Chard, & Tofts, 2004; Restom et al., 2007), SPECT (Slosman et al., 2001b) and PET (Bentourkia

et al., 2000b; Leenders et al., 1990b). Both CBF_0 and $CMRO_2$ influence the widely used BOLD-fMRI signal (Richard B Buxton, 2010) and are thus potential confounds in studies of cognition in aging using this signal.

5.2.1 Aging and cognition

Healthy aging is associated with cognitive losses; however, it is still debated whether age-related increases in reaction time in some specific tasks are merely a result of general slowing of information processing (Salthouse, 1996b) or if some specific deficits are disproportionately affected in the aging brain (R. L. West, 1996b). The so-called "frontal aging" theory links executive function loss to bio-physiological correlates in the frontal cortex, the control centre of executive function (Funahashi, 2001), but has nonetheless been questioned (Greenwood, 2000b; MacLullich et al., 2002b).

Repeatedly used for studying cognitive aging, the color-word Stroop task (Stroop, 1935) requires successful inhibition of task-irrelevant ("interfering") information, a facet of executive function. Typically, subjects are asked to identify the color of a word whose meaning is incongruent (e.g., "Blue" written in green ink). A large body of literature has associated aging with an increase in the interference effect of the incongruent stimuli (Bugg et al., 2007; MacLeod, 1991; Mathis et al., 2009; Milham et al., 2002; Prakash et al., 2009; Van der Elst et al., 2006; R. West & Alain, 2000). However several other studies (Langenecker et al., 2004; Schulte et al., 2009; Uttl & Graf, 1997; Zysset et al., 2006) and meta-analyses (Ben-David & Schneider, 2009; P Verhaeghen & De Meersman, 1998; Paul Verhaeghen & Cerella, 2002) have challenged this view. These contradicting results bring up questions about the diversity of mechanisms of cognitive aging. Could the diversity of observations be due to distinct aging mechanisms subsumed by physiological differences?

5.2.2 Vascular correlates of cognition in aging

Vascular correlates of cognitive impairments and dementias have long been noticed (Dickstein et al., 2010; Nagai et al., 2010). In healthy 65-75 year-olds, a relationship was recently established (Mozolic et al., 2010a) in a randomized intervention linking an increase in local CBF_0 in the

prefrontal cortex, despite constant gray matter volume, to improved cognitive performance. Heo et al. (Heo et al., 2010a) found a correlation between memory performance and hippocampal CBF_0 in older adults, also highlighting vascular correlates of cognition in aged adults and the importance of CBF_0 as a parameter to measure and control for. A recent study (Suhr & Chelberg, 2013) found an association between dorsolateral prefrontal cortex baseline oxygenation ($sO2_0$), number of hours of physical activity per week, and memory performance, but not executive function performance, in older adults.

Flow has also been studied during cognitive tasks, but studies combining BOLD and flow measurements of functional activation in the elderly have found conflicting results using different tasks and brain regions. Ances et al. (Ances et al., 2009b), using calibrated fMRI, found reduced BOLD amplitude but an unchanged number of activated voxels and fractional change in CBF and $CMRO_2$ in response to visual stimulation in the older group. In contrast, Restom et al. (Restom et al., 2007) found no significant age-related difference in BOLD amplitude despite an increased fractional CBF response to a memory task, consistent with an age-related increased $CMRO_2$ response. Recently Mohtasib et al. found an increased BOLD response with an unchanged CBF response to a Stroop task with aging, interpreted as a decrease in metabolism and neural activity (Mohtasib et al., 2012). From these glaring discrepancies, we argue that additional factors must be taken into account in aging studies. The apparent relationship of cognition with CBF_0 suggests that vascular physiology is a key factor.

5.2.3 Relationship between cardiovascular fitness and cognition in older adults

Exercise is known to have beneficial systemic effects on vascular function, for example by improving endothelial function (Di Francescomarino, Sciartilli, Di Valerio, Di Baldassarre, & Gallina, 2009; Joyner & Green, 2009) and reducing several peripheral risk factors associated with metabolic syndrome and inflammation, themselves associated with cognitive decline (Cotman et al., 2007). In healthy older adults, some longitudinal studies (Dustman et al., 1984; Kramer et al., 1999) as well as meta-analyses (S. Colcombe & Kramer, 2003) have concluded that aerobic fitness is associated with improved performance in executive control processes (see (Erickson & Kramer,

2009) for a short review). From this, together with the observed relationship between CBF_0 and cognition, it can be hypothesized that beneficial effects of exercise on cognition are mediated by vascular factors. Could uneven cardiovascular fitness play a role in the diversity of cognitive aging?

Morphological and vascular correlates of the potential effect of fitness on cognition have been investigated in humans. Increased middle cerebral artery mean flow velocity (MCAv) has been measured in individuals with higher VO_2max value (a "gold standard" indicator of cardiovascular fitness) (Ainslie et al., 2008). Active lifestyle has also been associated with improved baseline cerebral autoregulation and a better protection against hypoperfusion (Formes et al., 2009). VO_2max was correlated with cerebrovascular reactivity (the correlation between MCAv and end-tidal CO_2) in older adults, but not in young ones (Barnes et al., 2013). Shifts in patterns of functional activation in response to cognitive tasks have also been studied, finding that fitness was associated with decreased activations in some regions activated prior to training (Lustig et al., 2009).

However, the above results are mitigated by some meta-analyses which found no dose-response effect of exercise (Etnier et al., 2006) or a majority of non significant effects (Angevaren et al., 2008; van Uffelen et al., 2008), concluding that the data currently available cannot support the direct role of aerobic fitness as a predictor of cognitive performance. In the same trend, some longitudinal studies (Madden et al., 1989) did not detect any beneficial effects of aerobic training on cognition. Thus, a better characterization of the relationship between age, cognition and cardiovascular health is required.

5.2.4 Resting state connectivity

Resting state networks have also been a topic of great interest in recent neuroscience literature, including aging studies. (Andrews-Hanna et al., 2007) measured decreased functional connectivity of BOLD in the default mode network (DMN). In a CBF study (Y Hao et al., 2011), voxels with either strengthened or with weakened correlation with the posterior cingulate cortex, part of the DMN, were found when comparing young and aged resting-state flow time courses. Recently, (Voss et al., 2010) investigated the effects of an aerobic training intervention on BOLD

functional connectivity in 3 resting state networks in healthy older adults. They found that while connectivity decreased with age, exercise improved correlation strength in several regions of the DMN and Frontal Executive networks, and associated this with cognitive improvement in executive tasks. Cardiovascular exercise might thus have effects on the brain both on absolute value and time fluctuations of CBF.

5.2.5 Objective

In light of the many conflicting results reviewed above on the link between cardiovascular fitness, cerebral perfusion and cognition in healthy aging, we designed a study with a large set of measurements with the goal to investigate potential effects of cardiovascular fitness on brain perfusion and oxygenation at rest and in response to a cognitive task in aging. Fitness effects on baseline cerebral physiology and cognition, as well as on mediating the relationship between the two, were investigated. Precisely, three physiological variables were measured: CBF_0 (using Arterial Spin Labelling (ASL) MRI), HbT_0 and $SO2_0$ (using time-resolved optical spectroscopy), in subjects from two age groups, young and aged, who were classified according to their fitness level. Resting-state functional connectivity as well as response to a cognitive Stroop task were recorded with simultaneous BOLD and flow contrasts using ASL.

5.3 Methodology

5.3.1 Subjects and recruitment

Forty-three healthy adult right-handed volunteers participated in this study, divided in two age groups: 19 young adults (10 females, 18-30 years-old, mean age 24.4 ± 2.5) and 23 older adults (17 females, 62-72 years-old, mean age 67.6 ± 2.9). In both age groups, there was no significant difference between the ages of the males compared to those of the females, based on a 2-sampled t-test ($p > 5\%$). All subjects from the aged group also participated in a parallel study, some of whose results are published in (Gauthier et al., 2013). Exclusion criteria comprised any history of neurological, cardiovascular or respiratory disease, color-blindness, functional illiteracy, smoking, drug or alcohol problem, signs of early dementia as assessed by the Mini-Mental State Examination, and any serious contraindication to the practice of physical activity or MR imaging.

This study was approved by the institutional review board of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (UNF/CRIUGM) and that of École Polytechnique de Montréal. Written consent was obtained from all subjects prior to the study.

5.3.2 Fitness assessment (VO_2max)

The gold standard for quantifying cardiorespiratory fitness is maximal oxygen uptake ("VO_2max") (J. A. Davis, 2006), typically expressed in mL of O_2 uptake per kg of body mass per minute. A measure of VO_2max was obtained by direct measurement of expired gases during an incremented maximal effort test, which is considered more precise than indirect methods. Subjects pedalled on a stationary bicycle with increasing resistance until they reached their maximum power; the test stopped when the subject could not maintain the pedalling speed despite strong verbal encouragement. The respiratory gases were measured and analyzed using a commercial system (Moxus, AEI technologies, Illinois) to compute a VO_2max value as the oxygen consumption attained at the maximum effort and maintained over 30 seconds. When testing elderly subjects, ECG was continuously monitored and a physician was in the building and reachable at all times.

5.3.3 Time-resolved spectroscopy measurements

A homemade time-resolved spectroscopy (TRS) system was built following a setup very similar to that described in (Gagnon et al., 2008b). In summary, four pulsed lasers of wavelengths 690, 750, 800 and 850 nm injected light into the subject's head from an optical fiber held on the forehead. Four fibers at distances 10, 15, 25 and 30 mm from the point of illumination collected photons, which were counted by four single photon photomultiplier tubes during 300 seconds. This yielded a measurement of reflectance which was fitted by a double-layer analytical model (Gagnon et al., 2008b) of the diffusion equation in order to estimate the optical properties (absorption (μ_a) and scattering (μ_s) coefficients) of each layer. In this model, the first layer represents scalp, skull and CSF, so that the second layer results are referred to as "brain HbT_0" and "brain SO_{20}". We also computed the fit with a homogeneous model for comparison.

The first layer thickness was measured on the MR anatomical image of the subject's head. The absorption coefficient μ_a was related to the concentration (c) of the dominant absorbers in the brain, namely oxygenated (HbO) and deoxygenated (HbR) hemoglobin, using the values of extinction coefficients (ε) of each absorber at each wavelength (λ), which were taken from the literature (Prahl, s. d.), by inverting: $\mu_a(\lambda) = \Sigma_i \varepsilon_i(\lambda) \cdot c_i$. Because the subjects were at rest in a dark room during the experiment, this procedure gave measurements of absolute baseline concentration of HbO and HbR, or equivalently of baseline total hemoglobin concentration (HbT_0) and average cerebral tissue oxygen saturation (SO_{20}), with HbT = HbO+HbR and SO_2 = HbO/(HbO+HbR). The probe was positioned over the left frontal region of each subject.

5.3.4 MRI data acquisition

The data was acquired on a Siemens Trio 3T system at the Unité de Neuroimagerie fonctionnelle in Montreal. Each scan session consisted of a) one anatomical scan, b) one Stroop task run imaged using a standard BOLD-EPI sequence, c) two Stroop task runs imaged using an Arterial Spin Labeling (ASL) sequence, d) one ASL resting-state scan and d) one fully relaxed magnetization (M_0) scan.

The anatomical image was a T1-weighted MPRAGE sequence with isotropic resolution of 1 mm^3 on a 256x256 matrix, TE/TR/α = 2.98ms/2300ms/9°. For the young adults (N=19), an iPAT GRAPPA acceleration factor of 2 was used to lower acquisition time.

The sequence for BOLD imaging was gradient-echo-EPI with parameters TE/TR/α = 30/1010/60, on a 64x64 matrix. Most of the frontal, parietal and occipital lobes were imaged in 17 slices of 4 mm spaced by 1 mm, with 4 x 4 mm^2 in-plane resolution.

The ASL scan used a dual-echo, pseudo-continuous ASL (pCASL) sequence (Wu, Fernández-Seara, Detre, Wehrli, & Wang, 2007), with parameters TR/TE1/TE2/α = 3000ms/10ms/30ms/90°, 4x4 mm^2 in-plane resolution, 11 slices of 7 mm with 1 mm slice gap on a 64x64 matrix, covering the same field-of-view as the BOLD sequence; iPAT GRAPPA acceleration factor = 2, postlabeling delay = 900ms, 82 blocks of 20 Hanning window shaped RF pulses with duration/space = 500/360 μs, flip angle of the labeling pulse = 25°, slice-selective gradient = 6 mT/m, tagging duration = 1.5 s. The M_0 scan consisted of a single image acquired

with the same parameters as the ASL sequence except for the TR, which was very long (10 000 ms) to yield a measurement of the fully relaxed magnetization, and was used to calibrate the ASL measures to compute absolute CBF values (Wang et al., 2003b).

The protocol for the functional imaging experiments was a modified two-color Stroop task under an event-related protocol. The stimuli were color words whose screen color sometimes matched their meaning (congruent), and sometimes did not (incongruent). Subjects had to identify the color on screen while ignoring the word meaning. Neutral events were those where the color of the word matched its meaning; interference events were those where it did not. Switching events were a special case of Interference when the subjects were cued to state the meaning of the word while ignoring the ink color. The reaction time and accuracy (% of trials with right answer given) in interference and switching trials were used as indicators of cognitive performance in the analysis.

The event-related protocol consisted in 45 stimuli (15 of each condition: neutral, interference or switching) separated by randomly distributed intervals between 2 and 18 s (average 10 s), for a total duration of 600 s per run. Each stimulus consisted of a fixation cross displayed for 1 s and then a word displayed for 2 s, so that the time interval between 2 consecutive stimuli was between 5 and 23 seconds (average 13 s). The stimulus presentation was synchronized with the scans using TTL triggers. The software for stimuli presentation was written in Matlab (MathWorks, USA) using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997).

A resting-state ASL scan of 8 minutes (160 volumes) was also acquired during which subjects were instructed to fixate a cross and to stay still. For the first 7 subjects, this resting-state scan lasted 4 minutes (80 volumes). The resting-state data from one aged subject was rejected due to a large artifact in the images causing negative flow values in the analysis.

5.4 fMRI data processing

The raw data was motion-corrected, co-registered to the anatomical image, and spatially smoothed with a 10x10x16 mm^3 Gaussian kernel in SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, University College London). From the dual-echo pCASL sequence, two time courses were extracted. In an ASL sequence, a tagging pulse

eliminates the signal from moving spins in every other image, so that the difference between two consecutive images is proportional to the inflow of spins. The flow contrast was computed by subtracting each pair of consecutive images (2-1, -(3-2), 4-3, -(5-4),...) acquired with TE = 10 ms; the BOLD contrast was computed by averaging each pair of consecutive images acquired with TE = 30 ms. The resulting BOLD and flow time series were spatially normalised to the Montreal Neurological Institute (MNI) atlas space in SPM8 to allow group-level analysis.

Baseline cerebral blood flow (CBF_0) was computed as the average flow over the entire time course. The value was then converted to a quantitative CBF_0 map in units of mL/min/100g using the approach described in equation [1] in (Wang et al., 2003b) and assuming the same values for the parameters (T1 of arterial blood, tagging efficiency, blood/tissue water partition coefficient). Brain-average and gray-matter average values were computed for each subject by averaging the CBF_0 map over masks based on the segmentation of the anatomical T1-weighted image using the SPM8 tool New Segment. The gray matter mask was defined as the voxels with 80% or higher gray matter probability to minimize partial volume effects. A third mask, for a region-of-interest (ROI) in the left prefrontal cortex, was defined as a cubic 125-voxels region centered on MNI coordinates [-42, 4, 35] mm, which corresponded to the maximum of the group-level statistical map from the main effect of Condition in the Stroop task BOLD scan. This region overlapped the sensitivity region of the TRS probe placed over the left prefrontal cortex.

The resting-state data was analyzed in two steps. First, independent component analysis (ICA) was used to identify six resting-state networks (RSNs) at the group level using the NEDICA approach (NEtwork Detection using ICA, (Perlbarg et al., 2008)). Then the strength of the correlations in each of these six networks was assessed using seed-based correlations at the individual level and then compared between the two groups of subjects.

BOLD and flow time courses were concatenated to yield a time series of 3D images that was decomposed into twenty spatially independent components (ICs). The IC maps were scaled to Z-scores and spatially normalised to the MNI standard space using SPM2. The ICs from all subjects entered a hierarchical clustering procedure in order to identify group-level networks. Details of the NEDICA approach are found in (Perlbarg et al., 2008).

Upon identifying, at the group level, six networks known from literature (Damoiseaux et al., 2006; De Luca et al., 2006; Perlbarg et al., 2008), functional connectivity (FC) maps were computed for each subject using the REST toolbox (Song et al., 2011). A seed region was defined as an 8 mm radius sphere centered on the voxel with the maximal amplitude in the subject's IC map (corresponding to the highest weight in IC decomposition), from which a seed time course was computed. The correlation of this time course with each voxel time course yielded a FC map for each subject and each network. These maps were converted to Z-statistics using a Z-Fisher transform, and then entered a group level analysis defined in SPM8. A group-level ANOVA also allowed testing for differences in FC based on two factors: age and fitness.

The Stroop task scans were also analyzed in SPM8. After preprocessing as described above, the task response was analyzed using a general linear model (GLM) with 10 regressors corresponding to the 3 standard hemodynamic basis functions as well as 6 previously estimated movement parameters and a constant term. The GLM was run in a standard manner (e.g. for temporal filtering). The amplitude of the response to the first basis function (canonical hemodynamic response function) for each subject over all sessions was entered in a second-level group analysis. The design was a 3-way ANOVA with factors age (young / aged), fitness (high-fit / low-fit) and condition (neutral / interference / switching).

Behavioral results to the Stroop task performed in the scanner were analyzed using an ANOVA on the accuracy and reaction time as indicators of cognitive performance for each of the three runs for each subject. For 12 of the 129 scans, a technical problem prevented recording of the subjects' answers. Runs for which accuracy in neutral trials was 60% or lower, or percentage of answered trials was inferior to 50%, were rejected. Thus, 6 runs out of the 117 recorded runs were rejected, from 2 young subjects.

In all statistical tests used, a significance threshold of $\alpha = 5\%$ was used with family-wise error (FWE) correction for multiple comparisons used for imaging data, unless mentioned otherwise.

5.5 Results

5.5.1 Age and fitness effects on physiological variables

In each age group, the subjects were separated between high-fit and low-fit individuals by setting a threshold on VO_{2max} values. The threshold was chosen to minimize the variance in each fitness group (and thus maximize that between groups). The separation is shown in Figure 5-1. The results and conclusions did no change when using the median to split the groups.

	Young	Old
Age (years)	24.4 ± 2.5	67.6 ± 2.9
VO_{2max} (mL/kg/min)	38.3 ± 5.9	26.3 ± 5.2
LF VO_{2max}	31.3 ± 3.8	22.9 ± 2.2
HF VO_{2max}	43.8 ± 3.3	30.1 ± 4.0

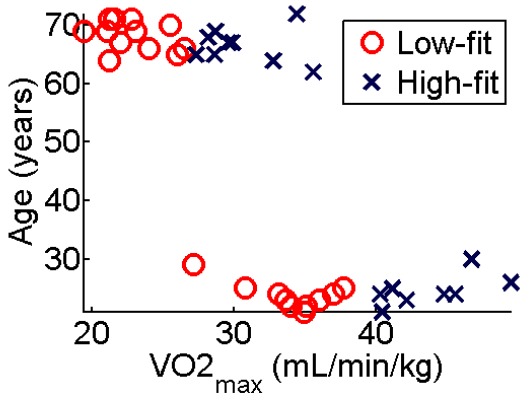

Fig. 5-1. Population statistics and separation between high- and low-fit based on VO2max measurement. LF: low-fit, HF: high-fit. Values are mean ± std.

In order to explore physiological bases of the variability in aging, seven variables were studied: HbT_0 and $SO2_0$ from the TRS homogenous model and from the 2-layer model (2^{nd} layer); whole brain and gray matter average CBF_0; and CBF_0 in a left prefrontal ROI centered on MNI coordinates [-42, 4, 35] mm, sometimes called the inferior frontal junction (Derrfuss et al., 2005). This ROI corresponded to the maximum on the statistical maps of the main effect of condition of the Stroop task in the group-level results from the BOLD scan, and coincided with the region probed by the TRS measurements. These seven variables were entered into an ANOVA with two categorical variables with two levels each: age (young / old) and fitness (high-fit / low-fit). The results are shown in Table 5.1. While age had a significant effect on all studied variables, there was no statistically significant effect of fitness on any of them (CBF_0, HbT_0 or $SO2_0$). Interaction effects were not significant.

Table 5.1: Mean values (2 columns on the left) and ANOVA p-values (2 columns on the right) for physiological variables.

	Young (mean ± S.E.M.)	Old (mean ± S.E.M.)	Age p-value	Fitness p-value
Brain CBF_0 (mL/100g/min)	**60.0 ± 2.9**	**48.5 ± 2.6**	**0.005***	0.36
Gray matter CBF_0 (mL/100g/min)	**76.3 ± 3.3**	**63.9 ± 3.3**	**0.012***	0.131
Left prefrontal CBF_0 (mL/100g/min)	**57.6 ± 3.4**	**47.5 ± 3.1**	**0.037***	0.148
Homog. HbT_0 (μmol/L)	**67.7 ± 4.4**	**53 ± 2.6**	**0.002***	0.567
Brain HbT_0 (μmol/L)	**68.1 ± 2.9**	**57.5 ± 2.8**	**0.02***	0.754
Homog. SO_{20} (%)	**65.7 ± 1.5**	**61.9 ± 0.8**	**0.031***	0.246
Brain SO_{20} (%)	**66.0 ± 1.2**	**62.1 ± 0.9**	**0.016***	0.45

BOLD and star symbol (*) denote statistically significant effect at $\alpha = 5\%$. Homog.: computed from homogenous model for TRS data; Brain: values from second layer of a two-layer model (see Methods). Interaction effects were not significant (not shown).

To further assess the potential relation of fitness to the physiological variables, we correlated each of the seven variables from Table 5.1 to the VO_2max within each age group. Among all, the two strongest correlations are illustrated in Fig. 5-2. The only one that was statistically significant was the correlation of SO_{20} with VO_2max in the older adults. There was a small non-significant correlation between HbT_0 and VO_2max in the young group. All other correlations of physiological variables with VO_{2max} were weak and non-significant ($|r| < 0.25$, $p > 25\%$). The

tendency of brain and left prefrontal CBF_0 and within the old group was towards an *inverse* correlation with VO_2max (r = -0.24, r = -0.23).

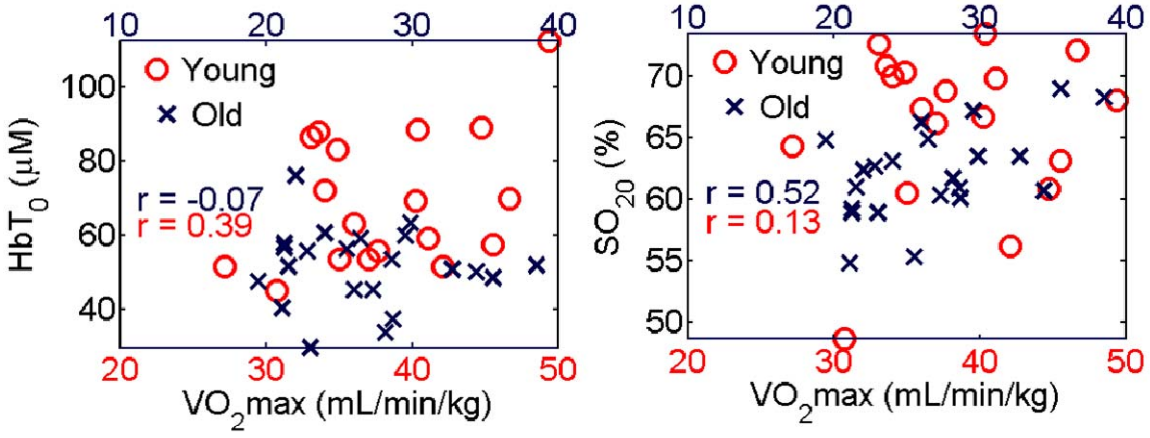

Fig. 5-2. Correlation between VO_2max and some of the physiological variables, within each age group. These were the two strongest correlations with VO_2max among all physiological variables (see Table 5.1). The only statistically significant correlation with VO_2max was that of SO_{20} in the old group (blue x's in the right image).

Spatial maps of CBF_0 were then compared between age groups, with results shown in Figure 5-3. Frontal regions as well the thalamus show higher CBF_0 in younger adults. There was no difference in CBF_0 when comparing high- and low- fitness groups, even at a threshold of $p < 0.001$ (uncorrected), neither over all subjects nor in each age group.

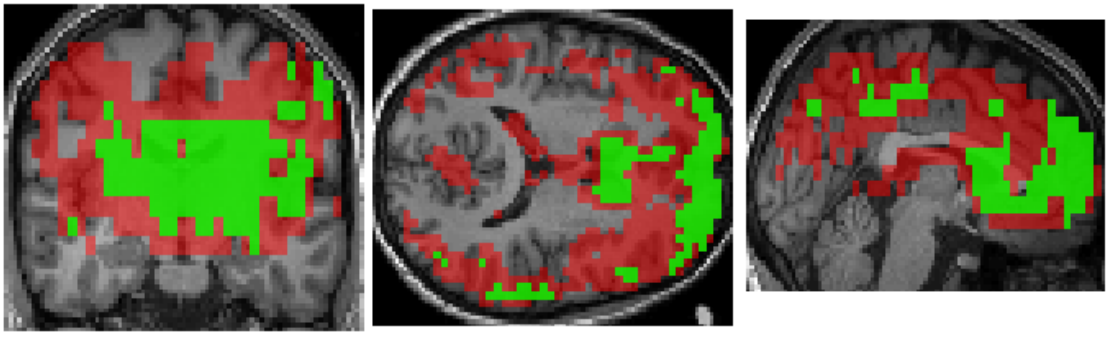

Fig. 5-3. Maximum intensity projections of thresholded t-statistic map for age comparison of CBF_0 (red: $p < 0.001$, uncorrected; green: $p < 0.05$ corrected for family-wise error): colored voxels exhibit larger CBF_0 in young than in older adults.

5.5.2 Resting state networks

Using the NEDICA resting state analysis approach, six known networks were identified from the concatenated time courses of BOLD and flow over all subjects: visual, associative visual, motor, default mode (DMN), dorsal attention and limbic (Figure 5-4, left column). For the default mode and dorsal attentional networks, two independent components were combined to generate the network map. The same networks were identified when using only the BOLD data (data not shown).

The time courses of BOLD and flow in each network were compared and temporally correlated. Older adults exhibited weaker correlation between BOLD and flow than young ones in both visual networks as well as dorsal attentional and DMN. In all networks, correlation was maximal for a 0 or -1 s delay (flow(t_i)*bold(t_i+1)) between bold and flow, which is to be expected given that flow is more arterial- and capillary-weighted and BOLD is more capillary- and vein-weighted since this is where most of the deoxyhemoglobin is found.

Using the IC maps to define seed regions, functional connectivity maps were computed for both BOLD and flow data separately. The Z-maps resulting from the group-level analysis are shown in Figure 5-4 (columns 2-4).

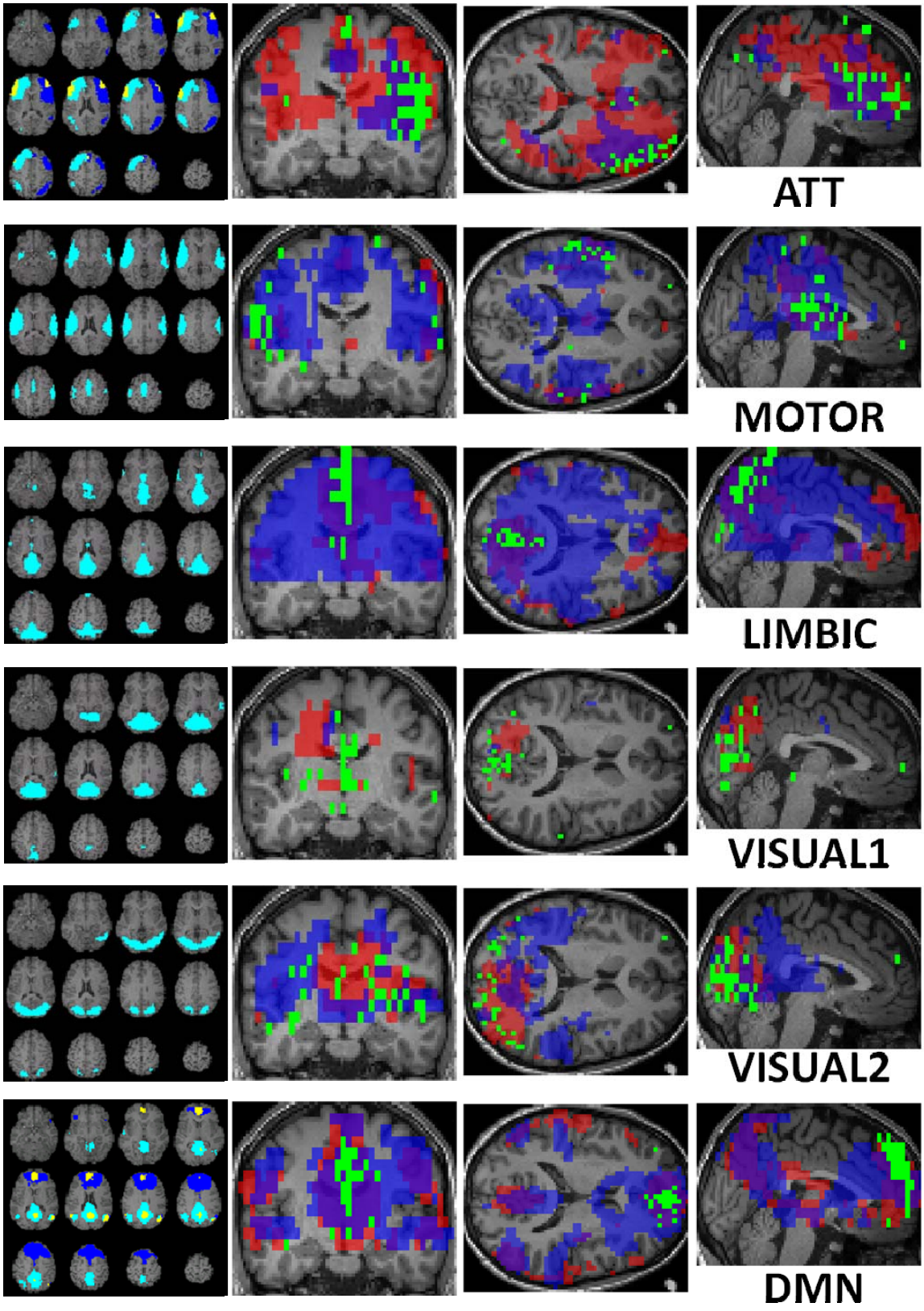
ATT
MOTOR
LIMBIC
VISUAL1
VISUAL2
DMN

Fig. 5-4. Left column: Six group-level classes of independent components identified using NEDICA, representing 6 known resting state networks and used to define seed time course for functional connectivity analysis. When two colors are displayed, the network was partitioned between two independent components in the decomposition. Columns 2-4: MIPs of functional connectivity maps overlaid on normalised anatomical image for the six seed regions selected. BLUE: maps computed from baseline BOLD data; RED: maps computed from baseline flow data. For display, the functional connectivity maps were thresholded at a very high significance threshold of $p \leq 1e\text{-}9$ (uncorrected for multiple comparisons). The green dots indicate voxels at the center of the seed regions (8 mm radius spheres) for each subject.

We then sought to quantitatively compare connectivity in the 6 networks between young and aged subjects. For this purpose, individual functional connectivity maps were Z-transformed and entered in an ANOVA with factors age and fitness. The DMN exhibited weaker flow (but not BOLD) connectivity in some frontal regions in the older adults, as shown in Figure 5. There were no significant differences in any other connectivity maps with height threshold $\alpha = 0.001$ and cluster threshold = 15.

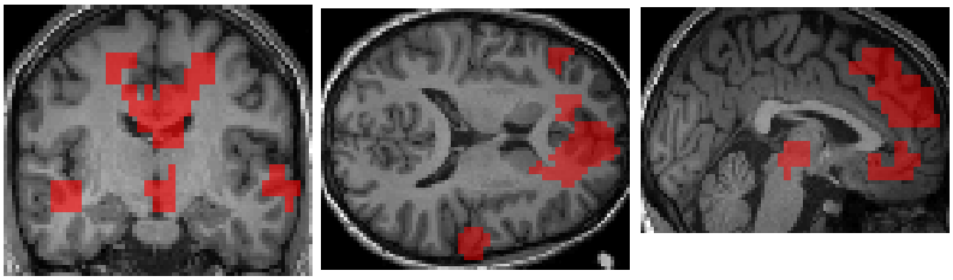

Fig. 5-5. Regions where flow functional connectivity is higher in young than in older adults (MIP overlaid on anatomical image), thresholded at $p = 0.001$ (uncorrected) and extent threshold = 15 voxels. The statistical comparison was computed over voxels in a mask defined by significant connectivity over all subjects at the group level. Only flow in the DMN exhibited age differences at this significance threshold.

5.5.3 Age and fitness effects on cognitive task

Table 5.2 shows the results of the ANOVA for the cognitive performance. There was a significant effect of age (with older adults being poorer performers) as well as an effect of condition (with increasing performance, on both reaction time and accuracy, from switching to interference to neutral trials (not shown)). When considering each run separately, there was a significant improvement of both reaction time and accuracy, but there was no interaction of this effect with age; all subjects got better at the task upon repetition. They had practiced the task once before entering the scanner. Interestingly, there was an interaction effect of age and fitness for reaction time. Post-hoc testing revealed that this interaction was due to the age-related slowing of reaction times being larger in the low-fit group (Figure 5-6) than in the high-fit group. All other interactions from the ANOVA were not significant (not shown). Reaction time and accuracy were inversely correlated (r = -0.54).

Table 5.2 - Behavioral results from Stroop task: p-values from ANOVA.

	Age	Fitness	Condition	Repetition	Age x Fitness	Age x Condition	Condition x Repetition
Reaction time – Each run	**3.0e-6***	0.15	**0***	**1.6e-8***	**9.5e-5***	0.44	0.98
Accuracy – Each run	**2.8e-4***	0.12	**3.2e-12***	**2.1e-4***	0.30	**0.001***	**0.017***
Reaction time – Average over runs	0.098	0.95	**4.7e-14***		**3.2e-4***	0.70	
Accuracy – Average over runs	**2.3e-4***	0.38	**8.5e-5***		0.54	0.15	

BOLD and star symbol (*) denote statistical significance at $\alpha = 5\%$.

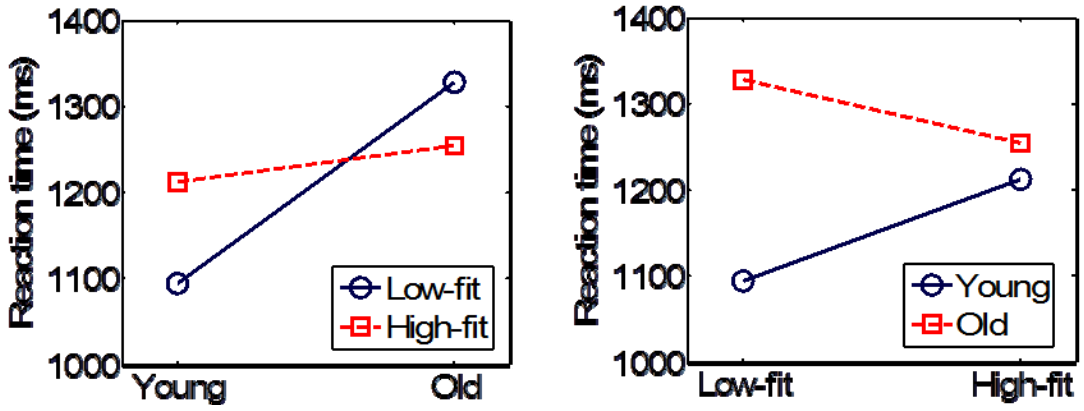

Fig. 5-6. Illustration of the age x fitness interaction on reaction times in the Stroop task. Illustrated value is the average over subjects of the mean reaction time over interference and switching trials. Left: the age-related slowing is larger in the low-fit group. Right: in the old group, fitness tends to improve performance (non-significant effect), but not in the young group.

5.5.4 Physiological variables and cognitive task

The correlation between cognitive results and physiological variables (CBF_0, HbT_0 and SO_{20}) was computed to investigate potential mechanisms for the observed age differences in cognitive performance. Results are shown in Table 5.3. The average reaction time and accuracy over all interference and switching trials were correlated with the physiological variables. There was a significant inverse correlation of reaction time with brain HbT_0 and SO_{20}. Furthermore, accuracy was correlated with SO_{20} and there was a nearly-significant trend (at α = 5%) with CBF_0 and gray matter CBF_0. When computing the same correlations separately in young and old groups, the correlation of SO_{20} with reaction time was significant (and almost significant for accuracy) only in the old group, but not in the young one. Curiously, in the young group (not shown in table 5.3), there was a small *inverse* correlation of accuracy with SO_{20} and HbT_0 (-0.37 and -0.35 respectively).

Table 5.3 - Correlation between cognitive performance and physiological variables.

Over all subjects	Correlation (r) with Reaction time	p-value	Correlation (r) with Accuracy	p-value
Brain CBF_0	-0.22	0.167	0.31	0.055
Gray matter CBF_0	-0.23	0.156	0.31	0.054
Left prefrontal CBF_0	-0.23	0.149	0.27	0.089
Homog. HbT_0	-0.21	0.184	0.22	0.173
Brain HbT_0	**-0.32***	**0.043***	0.17	0.296
Homog. $SO2_0$	**-0.39***	**0.013***	**0.32***	**0.043***
Brain $SO2_0$	**-0.42***	**0.007***	0.31	0.051
In aged subjects				
Brain CBF_0	-0.14	0.534	0.19	0.376
Gray matter CBF_0	-0.13	0.551	0.20	0.352
Left prefrontal CBF_0	-0.059	0.790	0.16	0.454
Homog. HbT_0	0.08	0.726	0.04	0.871
Brain HbT_0	-0.23	0.293	0.11	0.614
Homog. $SO2_0$	**-0.46***	**0.026***	0.41	0.053
Brain $SO2_0$	-0.30	0.160	0.24	0.262

BOLD and star symbol (*) denote statistically significant effect at α = 5%. Homog.: computed from homogenous model for TRS data; Brain: values from second layer of a two-layer model (see Methods).

5.5.5 Flow and BOLD response to Stroop task

The spatial patterns of BOLD and flow responses to the Stroop task were investigated using an ANOVA with factors condition, age and fitness. Results are shown in Figure 5-7. The Stroop interference effect activates bilateral frontal and parietal regions. Many regions show age-related

increases in BOLD response with age. Smaller, more subtle fitness effects are also seen in parietal regions where low-fit individuals exhibit larger BOLD responses.

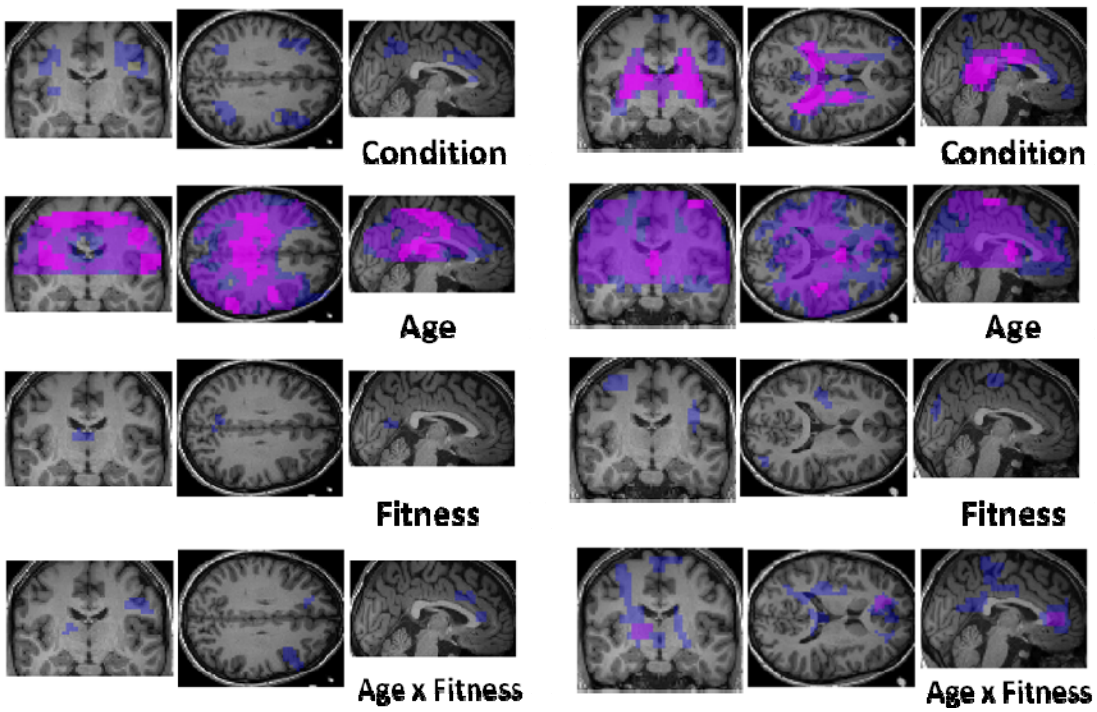

Fig. 5-7. ANOVA results for BOLD-EPI scan (left) and BOLD extracted from ASL (right). Post-hoc t-tests revealed the nature of the effect (in parentheses). 1st row: main effect of condition (switching > interference > neutral); 2nd row: main effect of age (old > young); 3rd row: main effect of fitness (low-fit > high-fit); 4th row: age x fitness interaction. Other interaction contrasts yielded no significant regions. Maximum intensity projections; color code: blue: $p < 0.001$ (uncorrected), pale magenta: $p < 0.05$ (FWE corrected), opaque magenta: $p <$ 1e-6 (FWE). Note that the left side appears on the right of the images.

The flow measurement during the Stroop task did not yield significant age, condition or fitness effects at $p < 5\%$ (FWE-corrected) nor $p < 0.001$ (uncorrected) (data not shown). As a control of the quality of the data, we observed that the main effect of the task (group effect for all conditions and all subjects pooled) showed significant activations only in the visual cortex. Since the BOLD contrast showed significant activations in many regions spanning the entire brain but with

maxima in the visual cortex, we suspect that the signal-to-noise ratio of flow measurements is too low for measuring small flow changes evoked by the task in other brain regions. We therefore chose to interpret the flow Stroop measurements with much caution and avoided drawing conclusions from those.

5.6 Discussion

5.6.1 Age, fitness and physiological variables

This study investigated vascular aspects of brain aging through measurements of cardio-vascular fitness, baseline optical measures, as well as blood flow and BOLD at rest and during a cognitive task. Two groups of young and older adults were separated into high- and low-fit individuals based on their VO_2max. The observed VO_2max decline with age was in concordance with previously reported declines of about 10% per decade (Betik & Hepple, 2008).

We measured a significant age-related decrease in brain-average, gray matter-average and regional baseline cerebral blood flow. Previous studies in similar age groups found comparable age-related decreases between 20-30% in global CBF_0 (Ances et al., 2009b; Parkes et al., 2004; Restom et al., 2007). (Asllani et al., 2009b) found a 15% decrease in gray matter CBF_0, similar to our 17% finding. The main regions in which perfusion was affected by age were in the frontal lobe and in the thalamus. (J Jean Chen, Rosas, & Salat, 2011) reports age-related declines in CBF in many cortical and subcortical regions including thalamus and frontal regions overlapping with our findings. (Parkes et al., 2004) also found decreases in middle, medial and superior frontal gyri as well as postcentral gyrus and inferior parietal lobule. Even after correcting for partial volume effect, (Asllani et al., 2009b) found age-related decreases in several subcortical and cortical and especially frontal regions, which spread to parietal regions in men.

The total concentration of hemoglobin HbT_0 is related to cerebral blood volume by the blood hemoglobin content (Huppert et al., 2009). The central volume principle (Richard B. Buxton, 2002b) linking CBF and CBV predicts CBF = CBV/τ, where τ is the transit time. However, accross all subjects, we found that HbT_0 was not significantly correlated with whole-brain nor gray matter CBF_0.

Both HbT_0 and SO_{20} were measured significantly lower in older adults. The mechanism for this decline could be brain atrophy or decreased vascular density. A change in hemoglobin content of blood would also affect measured HbT_0. Finally, it is possible that changes in the thickness and density of the different tissues of the head (skin, skull, brain) affect the optical properties and thus the measured HbT_0 (Bonnéry et al., 2012); but this effect should be less important when using the two-layer model, which also shows an age-related decline.

Our data showed no effect of fitness on CBF_0, HbT_0, or functional connectivity, despite significant age effects and a clear separation between high-fit and low-fit out of our 43 subjects. Though some animal studies point towards improvements in cerebral perfusion and blood volume with exercise, this effect remains to be established clearly in humans. Ainslie (Ainslie et al., 2008) found a significant association between fitness and flow velocity in the middle cerebral artery, but this association was not found in a recent study by another group (Barnes et al., 2013). In Burdette (Burdette et al., 2010), an aerobic exercise training of 4-months improved hippocampal CBF_0 and connectivity compared to a control group with non-aerobic and educational training. It is possible that if exercise has beneficial effects on the brain, these are subtle or region-specific.

5.6.2 Resting-state functional connectivity

Our simultaneous BOLD and flow recording using an ASL sequence allowed us to identify six networks previously observed in BOLD over our 43 subjects. Previous studies have measured decreased functional connectivity in the default mode network in healthy older individuals using BOLD (Andrews-Hanna et al., 2007) and flow (Y Hao et al., 2011). We measured this effect only in the flow data. We did not measure any significant effect of fitness on resting-state networks.

5.6.3 Cognitive task

Reaction time and accuracy in our modified Stroop task served as indicators of cognitive performance, more precisely of executive control. Analysis of the behavioral data showed a "Stroop effect", meaning that answers were slower and performance poorer in interference trials compared to neutral trials. However, the Stroop effect was not more important in older adults,

who generally performed less well in all conditions of the task. This argues against the frontal aging hypothesis discussed in the introduction.

As reviewed in the introduction, current literature shows a certain controversy on the nature and specificity of the effects of fitness on cognition. In concordance with previous studies in older adults (S. Colcombe & Kramer, 2003; Erickson & Kramer, 2009), our data showed a positive effect of fitness on cognitive performance measured by reaction time. This effect took the form of a "protection" against age-related slowing in the high-fit group. We investigated potential vascular correlates for this effect by studying spatial maps of regional CBF_0, but these did not yield significant differences between fitness groups. Thus, our data suggests that baseline perfusion is not the main mediator of the protective effect of fitness against cognitive slowing. Cognitive performance indicators were correlated with prefrontal HbT_0 and SO_{20} (and almost significantly with brain-average CBF_0). This correlation could be mostly explained by the effect of age (since both cognitive performance indicators and HbT_0, SO_{20} and CBF_0 were decreased in the older group). Nonetheless, when computed separately in each age group, SO_{20} was still correlated with cognitive performance in the old group, but not in the young one.

Flow and BOLD were measured during the Stroop task. Analysis of this functional imaging data highlighted the brain regions implied in switching and interference processing, related to executive control, in bilateral prefrontal cortex (inferior frontal junction). Our results confirm previous observations (Derrfuss et al., 2005; Laird et al., 2005). Some brain regions exhibited significantly higher BOLD contrast in older adults. However, flow contrast did not exhibit significant age, fitness or condition differences, perhaps because of the lower SNR of this measurement. A decrease in BOLD with unchanged CBF response would indicate a reduction in the metabolic response ($CMRO_2$), as hypothesized in (Mohtasib et al., 2012).

A left prefrontal region exhibited significant age x fitness interaction, and post-hoc testing revealed that low-fit older adults had significantly higher BOLD contrast in this region. It overlapped with the region of highest contrast for the main effect of Condition on the Stroop task, in the left prefrontal cortex (inferior frontal junction around coordinates [-42, 4, 35] mm). This observation suggests that fitness might have a "rejuvenating" effect on the brain, which might be related to poorer Stroop task performance of low-fit older adults compared to high-fit.

5.7 Conclusion

In summary, this study investigated some vascular correlates of aging and explored the hypothesis that cardiovascular fitness had an effect on cognition, mediated by changes in cerebral perfusion or oxygenation. Overall, older adults had lower total and gray matter CBF_0 as well as left prefrontal CBF_0, HbT_0 and SO_{20}, indicating reduced perfusion and oxygenation of the brain at baseline. The main left prefrontal region solicited by the interference effect of the Stroop task was also one where lower-fit older adults exhibited higher BOLD activity in response to the task. This is consistent with the hypothesis of a decrease in oxygen metabolism with aging which could possibly be prevented by maintaining good cardiovascular fitness. Age-related slowing of reaction times in the Stroop task was significantly reduced among high-fit individuals compared to low-fit. SO_{20}, but neither CBF_0 nor HbT_0, was correlated with VO_2max and with cognitive performance in aged adults. This suggests that cerebral oxygenation, rather than perfusion, is a significant correlate of the protective effect of fitness from cognitive decline. In light of this, time-resolved spectroscopy provides non-invasive optical measurements of SO_{20} which could be used as a covariate in future aging studies.

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CHAPITRE 6 ARTICLE 3 : MULTIMODAL STUDY OF THE HEMODYNAMIC RESPONSE TO HYPERCAPNIA IN ANESTHETIZED AGED RATS

Cet article vient compléter l'exploration des aspects vasculaires du vieillissement en liant des mesures micro et macroscopiques. Il présente, dans une court article (*letter*), des mesures de la réponse hémodynamique à l'hypercapnie chez des rats jeunes et âgés. Les mesures sont obtenues via plusieurs modalités d'imagerie : en IRMf (contraste BOLD), en IOI (réponse HbO, HbR et HbT) et en FGL (débit) ainsi qu'en MBP (vitesse du débit et diamètre dans des vaisseaux individuels). Les réponses des différentes modalités sont comparés entre elles et entre les groupes d'âge. Le manuscrit a été soumis à *Neuroscience Letters* le 25 novembre 2013 et, au moment de soumettre cette thèse, est en attente de réponse de la part des éditeurs.

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6.1 Abstract

With aging, the brain undergoes changes in metabolism and perfusion, both of which influence the widely used blood-oxygenation-level-dependent (BOLD) MRI signal. To isolate the vascular effects associated with age, this study measured the response to a hypercapnic challenge using different imaging modalities in 19 young (3 months-old) and 13 old (24 months-old) Long-Evans rats. Intrinsic optical imaging was used to measure oxy (HbO), deoxy (HbR) and total (HbT) hemoglobin concentration changes, laser speckle for cerebral blood flow (CBF) changes, and MRI for the BOLD signal. Older rats

had smaller HbO (41% smaller), HbT (50%) and CBF (34%) responses, but the temporal dynamics did not exhibit significant age differences. The ratio of CBV to CBF responses was also smaller in older adults, potentially indicating a change in the compliance of vessels.

Keywords— BOLD fMRI; intrinsic optical imaging; laser speckle; two-photon microscopy; cerebral blood flow; aging; hypercapnia; rat

6.2 Introduction

Aging, even in health, is associated with various alterations in brain structure and function. Many neuroimaging studies have tried to characterize the effects of aging on the brain using different imaging techniques. The most popular of these is probably the Blood Oxygenation Level Dependent (BOLD) magnetic resonance imaging (MRI) signal (Ogawa et al., 1992), thanks to its capacity to map brain activity in a whole-brain field-of-view non-invasively with millimetric resolution. However, the interpretation of BOLD measures is not straightforward, as the signal results from a complex interplay between metabolic and vascular responses (Richard B Buxton, 2010).

Studies have shown that aging leads to modifications in brain oxygen metabolism (Leenders et al., 1990a; Marchal et al., 1992) , blood volume (Leenders et al., 1990a; Y. Zhang, Peng, Chen, & Chen, 2010b) and flow (Ances et al., 2009a; Asllani et al., 2009a; Bentourkia et al., 2000a; Biagi et al., 2007a; Leenders et al., 1990a; Restom et al., 2007; Slosman et al., 2001a), all of which have a direct influence on the BOLD signal. Thus, a measured difference in BOLD can lead to different interpretations, and past aging studies have failed to find consensus on the BOLD and CBF responses to cognitive tasks (for example, compare (Ances et al., 2009a; Mohtasib et al., 2012; Restom et al., 2007)).

This study was designed to respond to a need for disentangling the effects of metabolic and vascular age differences, by measuring a "purely" vascular response using a collection of imaging modalities to separately measure flow, volume and a correlate of oxygenation. Towards this goal, a hypercapnic stimulus was chosen, as it is commonly assumed that mild hypercapnia evokes little or no metabolic response (T. L.

Davis et al., 1998; Hoge et al., 1999b) while it provokes vascular dilation and increases perfusion without spatial specificity.

The goal was thus to compare between two groups of rats, young adult and old, the evoked response to hypercapnia in terms of 1) cerebral blood flow (CBF) using laser speckle imaging; 2) total, oxy- and deoxy-hemoglobin using intrinsic optical imaging and 3) the BOLD-fMRI signal. We also aimed at measuring single-vessel response at the microscopic level using two-photon microscopy (TPM) in the same animals. We hypothesized that the differences between age groups would be reflected in the vascular response to hypercapnia, which could help disentangle the different contributions to the BOLD signal differences reported in neuroimaging literature.

6.3 Methodology

6.3.1 Animal preparation

Thirteen old (23-25 months-old: O) and 19 adult (11-15 weeks-old: Y) male Long-Evans rats were used in this study. All procedures were approved by the animal ethics committee of the research center of the Montreal Heart Institute. The housing conditions and surgical procedures were described in a previous publication of a study using the same animals (M Desjardins, Berti, Lefebvre, Dubeau, & Lesage, s. d.).

For all three modalities (BOLD, IOI-speckle and TPM), the stimulation protocol was an alternation of hyperoxic (baseline) and hyperoxic + hypercapnic (hypercapnia) episodes. The baseline between hypercapnic episodes was pure O_2 in order to maintain the rats in their best health for long duration experiments (6-12 hours for IOI and TPM). At baseline, animals received 2L/min pure O_2 through an open face mask. The hypercapnic episodes consisted of 30-seconds periods of 7% CO_2 in pure oxygen, followed by 90 seconds of baseline. Each scan lasted 12 minutes with hypercapnic episodes starting at times 30, 150, 270, 390 and 510 s. For IOI and BOLD-fMRI, an extra one-minute of baseline was added at the beginning to visualize a clear baseline. The rat physiological parameters (respiration, heart rate, arterial blood pressure (except for fMRI) and temperature) were continuously monitored and recorded.

6.3.2 MRI setup, acquisition and processing

A subset of the animals (12 old, 12 young) underwent MRI scans 1 to 21 days before the IOI-speckle-TPM experiments. Among these, two of the old animals were excluded from the analyses because they died prematurely, after the MRI but before the IOI experiment. MRI scans were done in a 7 Tesla (Agilent, CA, USA) MR scanner, with a 30 cm bore and a gradient insert with 600mT/m maximal slope. Rat noses were placed into a cylindrical tube for anesthesia that limited head movement. Anesthesia was maintained with 2-3% isoflurane at 2 L/min in pure O_2. Rats were maintained at 37 °C and rectal temperature and respiration rate were recorded (Small Animal Instruments, NY, USA). Excitation pulses were produced with a 2-channel resonator with 7 cm internal diameter (Rapid MR, Germany). For reception, a 4-channel mouse heart coil (Rapid MR) was positioned over the rat heads, fitting snugly. High resolution anatomical images were generated using a fast spin echo sequence (FSEMS) with 12 slices of 1 mm thickness, 256 x 256 matrix, 36-40 mm FOV centered over the brain, 8 echo train length and 4 averages. For fMRI, single-shot gradient echo EPI were recorded using the EPIP sequence with the same slice plan, 64 x 64 matrix, with a 1 second TR, leading to one volume every 2 seconds. 330 volumes were acquired. For each rat, the BOLD time course was band-pass filtered between 0.005 and 0.1 Hz to remove long-scale drifts and some of the noise. The time course was then separated in blocks of 120 seconds corresponding to each 30 s period of hypercapnia followed by 90 seconds of return to baseline, then averaged over blocks after linear detrending.

6.3.3 Intrinsic optical imaging setup, acquisition and processing

The intrinsic optical imaging (IOI) and laser speckle system was custom-built and the analysis was performed using an in-house toolbox. The setup and processing methods are identical to those described in previous papers (Dubeau, Ferland, et al., 2011; Guevara, Pouliot, Nguyen, & Lesage, 2013). The IOI data yielded measurements of the micromolar (μM) changes in concentration of HbO, HbR and HbT, assuming baseline concentrations of 60, 40 and 100 μM to compute effective extinction coefficients. Assuming

constant hematocrit, relative changes in HbT were interpreted as changes in CBV. The laser speckle measurement yielded changes in CBF relative to baseline.

A time course was extracted for each modality (HbO, HbR, HbT, CBF, BOLD) and averaged over the 5 blocks of hypercapnic episodes. The maximum percent change and time-to-peak were determined as the maximum of the block-averaged curve for each animal. The ratio of CBV to CBF percent changes (HbT/HbT_0) / (CBF/CBF_0) was also computed. The maximum change, time-to-peak and ratio were compared between age groups using two-sample t-tests.

6.3.4 Two-photon microscopy setup, acquisition and processing

Measures were made on a custom-built two-photon microscope controlled by a LabVIEW interface (National Instruments, TX, USA). The setup has been described elsewhere (M Desjardins et al., s. d.).

For each animal, a picture of the craniotomy along with the real-time display of the surface vessels scanned were used to localize one arteriole and one venule and guide manual positioning of line scans across and along targeted vessels. Thus, each vessel was scanned both perpendicularly (to measure diameter) and longitudinally (to follow red blood cells movement and compute speed). Because the contrast agent is contained in blood plasma, red blood cells (RBCs) appear as dark spots inside the vessels. Following the movement of those spots through successive line scans over the same region is the principle for measuring RBC speed (Kleinfeld et al., 1998). These line scans measured 200 points along a variable-length (~25 μm) line at a rate of 400 kHz (line-rate = 2 kHz), alternating between the perpendicular and longitudinal scans of the same vessel. In each animal, one arteriole and one venule were scanned continuously, alternating 40 perpendicular and 40 longitudinal scans, during one 12-minute hypercapnia/normocapnia paradigm.

All analyses were performed in Matlab (MathWorks, MA, USA) using in-house code. The detailed processing methods have been described elsewhere (M Desjardins et al., s. d.). The time courses for speed and diameter were averaged over all CO_2 blocks like for the other modalities.

6.4 Results

The mean block-averaged curves are shown in Figure 6-1. The response curves are observed to have similar shapes but different amplitudes between the age groups.

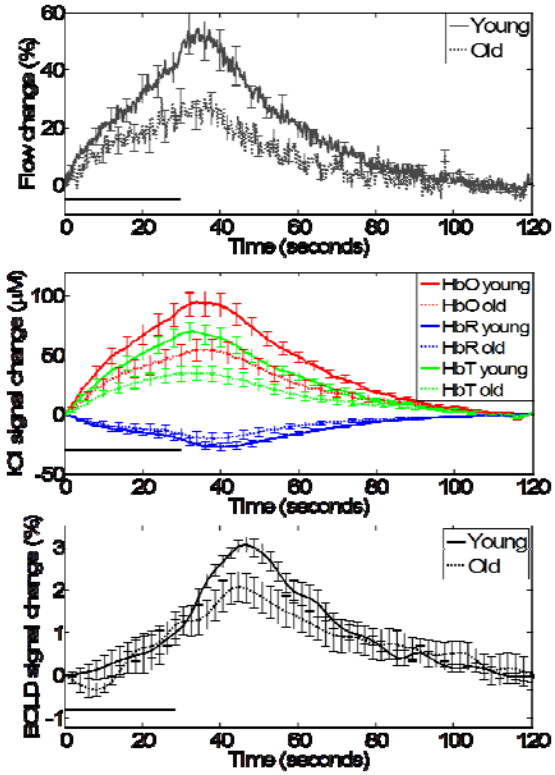

Fig. 6-1. Age group- and block- averaged responses to hypercapnia. The black line from 0-30 s represents the presence of 7% CO_2 in breathed O_2. Error bars are S.E.M. Top: flow from laser speckle, middle: IOI signals, bottom: BOLD-MRI.

The mean values over each age group are provided in Table 6.1 and compared using two-sampled t-tests. While there appears to be no difference in the temporal dynamics, the maximum change in HbT was significantly lower in the younger group ($p < 0.05$, Bonferroni-corrected). HbO and CBF also showed similar trends ($p < 0.05$, uncorrected). The $\Delta CBV/\Delta CBF$ ratio was also lower in the older group.

Table 6.1: Comparison of response amplitude and time-to-peak in the two age groups

	YOUNG (mean ± S.E.M.)	OLD (mean ± S.E.M.)	p (unc.)	p (Bonf.)
IOI-speckle	**(N = 19)**	**(N = 13)**		
HbO μM change	100.9 ± 10.0	59.4 ± 10.7	**0.01***	0.10
HbO τ_{peak} (s)	37.0 ± 1.4	33.4 ± 2.6	0.20	2.19
HbR μM change	-29.0 ± 3.0	-23.4 ± 5.4	0.33	3.66
HbR τ_{peak} (s)	41.7 ± 1.5	44.5 ± 6.3	0.62	6.80
HbT μM change	**74.9 ± 7.8**	**37.6 ± 7.1**	**0.001***	**0.02***
HbT τ_{peak} (s)	33.7 ± 1.3	39.3 ± 5.6	0.27	2.92
CBF % change	71.6 ± 7.3	47.1 ± 5.7	**0.02***	0.22
CBF τ_{peak} (s)	34.6 ± 1.3	34.1 ± 3.3	0.86	9.49
ΔCBV/ΔCBF ratio	1.07 ± 0.02	0.76 ± 0.09	**0.008***	0.0847
MRI	**(N = 12)**	**(N = 10)**		
BOLD % change	5.6 ± 0.7	4.6 ± 1.1	0.43	4.77
BOLD τ_{peak} (s)	43.2 ± 3.2	60.0 ± 10.9	0.13	1.40
	Only responding (N=8)	**Only responding (N=5)**		
BOLD % change	5.9 ± 0.6	5.9 ± 1.8	0.99	10.90
BOLD τ_{peak} (s)	46.0 ± 1.8	44.3 ± 4.8	0.70	7.73

BOLD characters and star (*) symbol denote statistically significant difference between age groups. p-values are presented both uncorrected (unc.) and Bonferroni-corrected (Bonf.). τ_{peak}: time-to-peak of the response relative to the onset of hypercapnia. "Only responding": in this section, only the rats showing a significant elevation in BOLD signal in response to hypercapnia are included.

To explore the microscopic correlates of the IOI and BOLD observations, we measured the response to hypercapnia in individual surface vessels using TPM. Figure 6-2 shows the speed responses in individual vessels (16-60 μm diameter) from 14 rats (6 young, 8 old). Only vessels for which there was a complete (5 hypercapnia blocks) recording are shown, as in other cases movement prevented a complete recording when the vessel fell out of the field-of-view. The diameter changes were also measured in the same vessels and are shown in Figure 6-3. Even though speed increases were consistently observed, diameter increases

were only seen in some of the arterioles and venules. We did not compute group-averages or test for differences in the TPM data, as they were taken from inhomogeneous vessel types (arterioles and veins) and calibers (16-60 μM), especially considering that relative changes are correlated to baseline values (see next paragraph).

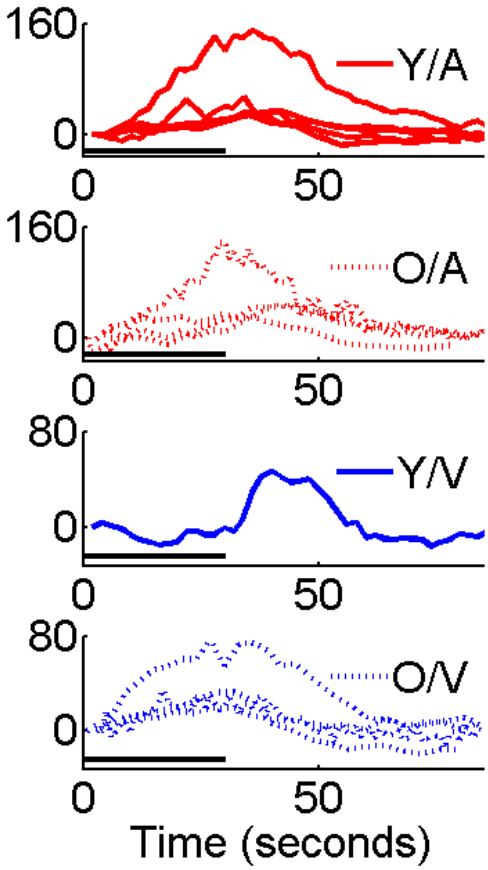

Fig. 6-2. Measured speed increase (y-axis units are % change relative to baseline) in individual surface vessels. Y/A: young rats, arterioles; O/A: old rats, arterioles; Y/V: young rats, venules; O/V: old rats, venules. The black trait indicates the period of hypercapnia (7% in breathed O_2).

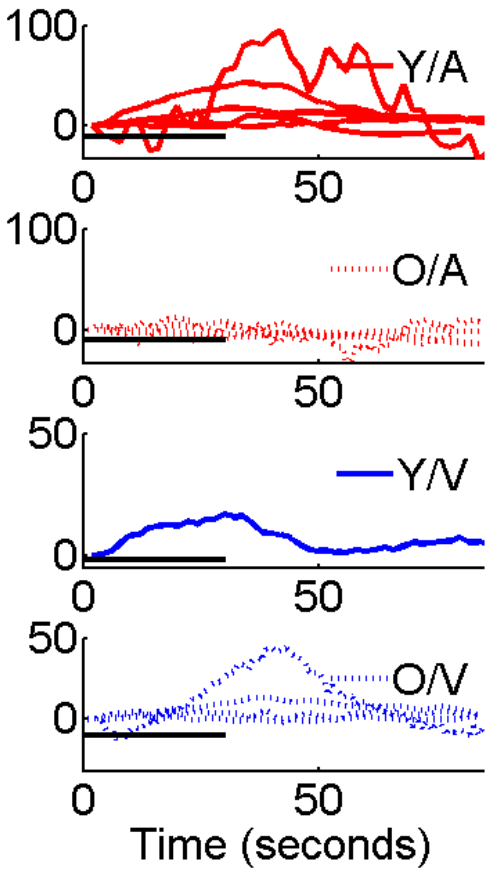

Fig. 6-3. Measured diameter increase (y-axis units are % change relative to baseline) in individual surface vessels. Y/A: young rats, arterioles; O/A: old rats, arterioles; Y/V: young rats, venules; O/V: old rats, venules. The black trait indicates the period of hypercapnia (7% in breathed O_2).

We then investigated correlations between the different measurements of the hemodynamic response. There was a strong correlation between HbO and CBF percent change across animals ($\rho = 0.86$, $p < 10^{-6}$). However, we did not find a correlation between BOLD and HbR response amplitudes, contrary to predictions from a BOLD signal model (Obata et al., 2004).

At the single vessel level, there was a significant inverse correlation between baseline speed and relative speed increase with hypercapnia over all measured vessels (Spearman's $\rho = -0.61$, $p = 0.02$), as well as between baseline diameter and relative diameter increase ($\rho = -0.76$, $p = 0.002$). There was no significant

correlation (ρ = -0.14) between the time-to-peak measured in individual vessels (speed time-to-peak) and that of CBF, perhaps because of the small number of measurements of the former.

6.5 Discussion

This study measured the response to hypercapnia in young and old rats and found smaller CBF, HbT and HbO responses in the old group. There was a similar trend of age-related decrease in the HbR and BOLD data, but it was not significant. HbO and CBF response amplitudes were correlated, while HbR and BOLD were not. A previous study in human found a temporal correlation of BOLD and HbR time courses which were measured simultaneously (Huppert et al., 2006). In our study, intra-subject variability of the responses measured on different days (Leontiev & Buxton, 2007) might explain the lack of correlation. The lower signal-to-noise ratio of BOLD measurements might also explain non-significant results.

In a previous study, IOI and laser speckle were used during somatosensory stimulation in young and aged rats (Dubeau, Ferland, et al., 2011). There, rats were of the LOU/c strain, which is known to be a model of healthy aging. Though the stimulation type and rat strain differed, both the previous and the present study observed reductions in CBF and IOI signal amplitudes with aging. Using FAIR MRI, (Mitschelen et al., 2009) also found significantly lower CBF responses to hypercapnia in older rats (~10% increase vs 50% in young rats). These studies support our observation that the CBF response to hypercapnia is reduced in aging, which might indicate reduced vascular reactivity (Lu et al., 2011).

In humans, previous studies have found conflicting results regarding the CBF and BOLD response to hypercapnia. Similar to our results, (Gauthier et al., 2013) found smaller CBF and BOLD responses in older adults. However, (Ances et al., 2009a) measured *larger* CBF increases in older adults (79% against 47% in young) with smaller BOLD responses. Our results support those of the former study.

Smaller relative flow changes in old rats could reflect similar absolute changes with higher baseline values. Indeed, in a previous study of capillary flow in the same animals, we found higher blood speed and diameter in the capillaries of the older rats (M Desjardins et al., s. d.). However, the lower density of

capillaries found in the same studies could account for lower global flow, in concordance with previous studies of aging. Isoflurane was also shown to affect baseline flow (Todd & Weeks, 1996) with baseline CBF twice as high as with other anesthetics.

The inverse correlation of the response amplitude (in %) with the baseline diameter and speed is in concordance with previous studies which found decreased heterogeneity of individual vessels' flows in response to hypercapnia (Hutchinson et al., 2006; Jespersen & Østergaard, 2012). In some of the measured vessels, we observed no change in diameter in response to hypercapnia. The lack of dilation observed in some vessels where speed increased during hypercapnia could be interpreted as a result of dilation happening upstream of the measured vessel.

Lower Δvolume/Δflow ratios in older subjects has previously been measured in response to sensory stimulation in rats (Dubeau, Ferland, et al., 2011). Smaller volume change for a given flow change suggests smaller compliance or higher rigidity of the vessels to CO_2-induced dilation. Previous studies have suggested compliance changes of cerebral vessels with aging (Dubeau, Ferland, et al., 2011; Dubeau, Desjardins, et al., 2011) and disease (Baraghis et al., 2011; Bolduc et al., 2011), but the nature and impact of these changes still remains to be elucidated. Indeed, Dubeau et al.'s results also suggested lower compliance in the healthy aged Lou/c rats in response to stimulation, while the two latter studies found increased compliance in response to heart-beat driven pressure changes. Given the large difference in time scales of these measurements (100 ms vs 20 s), it is possible that "active" versus "passive" (inflation of a vascular "balloon") dilation lead to distinct compliances, as suggested in a model by Behzadi et al. (Behzadi & Liu, 2005).

Some limitations must be mentioned upon interpreting our results. First, the relative changes in CBF and HbT are subjects to systematic confounds. The speckle pattern includes both static and moving scatterers, so that there is partial volume effect which underestimates the real flow (Luckl et al., 2010). Also, in our combined IOI-speckle setup, the camera aperture is adjusted to a compromise between both modalities (IOI and speckle) and thus is not optimized for speckle measurements, which also leads to an

underestimation of flow changes. Isoflurane has been shown to more than double the baseline CBF and to also affect CBV (Todd & Weeks, 1996) compared to other anesthetics, so that relative changes might be underestimated. However, these potential errors in the absolute values should not influence the age group comparisons since they are expected to affect all measures in a similar way. Lastly, in addition to being a vasodilator, isoflurane is known to influence neurovascular coupling (Franceschini et al., 2010) and thus potentially flow dynamics, relative to the awake state. Chronic preparations to measure blood flow in awake animals (Shih et al., 2012) may be required to remove anesthesia confounds.

In conclusion, this study provided multimodal measurements of the response to hypercapnia in young and old rats. In the old rats, smaller flow and volume increases were measured, suggesting differences in vascular reactivity and vessel compliance. In the future, similar studies in the awake animal could help further our understanding of the dynamics of flow in aging and pathology.

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6.7 References

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CHAPITRE 7 DISCUSSION GÉNÉRALE

Les travaux de cette thèse se sont intéressés au vieillissement cérébral en ciblant surtout ses effets vasculaires à l'échelle microscopique (vaisseaux sanguins individuels) et macroscopique (cerveau entier), faisant usage de multiples techniques d'imagerie complémentaires. Trois articles scientifiques ont été rédigés pour présenter les résultats de trois études menées d'une part chez l'humain, et d'autre part dans un modèle animal, le rat. Un retour sur les objectifs initialement fixés, la validation/réfutation des hypothèses et quelques éléments de réflexion sont présentés dans cette section.

7.1 Premier objectif

Le premier article de cette thèse a effectivement répondu à l'objectif correspondant, en rapportant les mesures de vitesse des globules rouges, de diamètre et d'hématocrite dans près de mille capillaires mesurés chez 12 rats jeunes et 12 rats âgés. Étant donné que la littérature prédit une diminution du débit sanguin cérébral avec l'âge, notre hypothèse initiale prévoyait mesurer des débits (vitesse x aire) inférieurs dans les capillaires du groupe âgé. Pourtant, les résultats ont révélé une augmentation sans équivoque de la vitesse (48%) et du diamètre (7%) des capillaires individuels chez les rats âgés par rapport aux jeunes. C'est pour cette raison que nous avons aussi mesuré la densité des capillaires, afin de relier nos observations à celle d'une diminution du débit global à grande échelle mesurée dans plusieurs études de la littérature. Nous avons effectivement mesuré une diminution de la densité des capillaires (20%), ce qui pourrait résulter en une diminution de la perfusion. Les résultats de notre étude remettent donc en question les mécanismes de la diminution de la perfusion avec l'âge. Nos données suggèrent que c'est la baisse de densité vasculaire qui en serait responsable. La prudence est donc de mise dans l'interprétation des mesures macroscopiques du débit.

Afin de lier nos mesures microscopiques avec les données macroscopiques de la littérature (Ances et al., 2009a; Asllani et al., 2009a; Bentourkia et al., 2000a; Biagi et al., 2007a; Leenders et al., 1990a; Restom et al., 2007; Slosman et al., 2001a) et du second article, il faudrait répéter l'étude en obtenant une mesure du débit sanguin cérébral macroscopique sur les rats, par exemple en IRMf-ASL (nous ne possédions pas cette séquence au moment d'effectuer les mesures).

Il y a toutefois une notion importante à souligner en ce qui a trait aux mesures du débit. Le débit est une mesure du volume de sang qui traverse un vaisseau ou un organe par unité de temps (unités de volume / temps). Il peut être calculé comme le produit de la vitesse du sang par l'aire du vaisseau, comme dans le cas de nos mesures en MBP. En revanche, la perfusion représente le débit sanguin par unité de volume ou de masse. La mesure obtenue par IRMf-ASL, qui en est une de perfusion, décrit donc l'apport de sang au tissu cérébral. Les deux mesures (débit et perfusion) sont reliées à l'apport de nutriments et d'oxygène aux cellules du cerveau, mais de manière différente. La vitesse du débit influence le temps de transit du sang dans les capillaires, donc l'extraction d'oxygène et de nutriments du sang par diffusion vers les tissus (Jespersen & Østergaard, 2012). La perfusion, quant à elle, décrit la quantité de sang qui traverse chaque gramme de tissu et peut donc alimenter les cellules.

La comparaison entre la mesure IRMf-ASL de perfusion et la mesure microscopique en MBP n'est donc pas directe. Par contre, il serait possible de modéliser la diffusion d'oxygène et de nutriments dans le tissu en utilisant des modèles de type Réseau Vasculaire Anatomique (RVA) (*Vascular Anatomical Network* en anglais) (David A Boas et al., 2008; Fang et al., 2008) afin de générer une mesure de perfusion à partir des données microscopiques de MBP. Un travail en ce sens a été réalisé par des collègues récemment (travaux non encore publiés). Pour exploiter nos données, il serait intéressant de modéliser l'effet sur la perfusion de la baisse de densité vasculaire, en utilisant des angiogrammes mesurés chez les rats âgés pour définir le réseau RVA modélisé, pour vérifier si nos données prédisent bien les résultats macroscopiques de la littérature.

Du côté expérimental, nous retenons de ce travail l'importance cruciale d'une bonne préparation chirurgicale pour assurer des données de qualité. Tous les paramètres physiologiques (pression artérielle, gaz sanguins (P_aO_2, P_aCO_2), ECG et respiration) sont autant de paramètres à mesurer, car ils sont susceptibles d'influencer la dynamique vasculaire. Certainement, le fait d'avoir laissé les animaux anesthésiés respirer librement plutôt que de les ventiler via une trachéotomie (Short, 1987) est susceptible d'introduire une variabilité, par exemple si les rats âgés respiraient plus lentement que les jeunes. Toutefois, d'après nous, cet effet est désirable puisqu'il reflète une variabilité naturelle entre les jeunes et les âgés, représentative de l'état physiologique réel. Cette variabilité deviendrait un facteur confondant si l'effet de l'anesthésie était différent en fonction de l'âge des animaux.

En effet, une des limitations principales de cette étude est l'effet possible de l'anesthésie sur le débit sanguin. Pour s'en affranchir, il faudra faire des mesures biphotoniques sur le rat éveillé en ayant recours à une préparation chirurgicale chronique, tel que discuté dans (Shih et al., 2012) par exemple. Il s'agira probablement de la prochaine étape pour notre groupe de recherche.

7.2 Second objectif

Nous avons atteint le second objectif d'investiguer les corrélats vasculaires du vieillissement cognitif en mesurant une panoplie de variables hémodynamiques chez des humains jeunes et âgés, classifiés selon leur niveau de forme cardiorespiratoire. Toutes les mesures de la physiologie de base (DSC_0, HbT_0 et sO_{20}) ont montré des différences significatives dues à l'âge, ce qui souligne l'importance de mesurer ces variables lors d'études d'imagerie utilisant des techniques hémodynamiques pour comparer des groupes hétérogènes. La mesure du DSC s'ajoute aisément à des études d'IRM à condition de disposer d'une séquence d'ASL, qui permet de le mesurer en quelques minutes seulement (3-4 minutes). Même si nos résultats n'ont pas démontré de corrélation du DSC_0 avec la performance à la tâche Stroop, plusieurs études passées ont établi un lien entre le DSC_0 dans certaines régions et d'autres aspects de la cognition (par exemple la mémoire (Heo et al., 2010a)). Nous croyons donc qu'il ne faut pas rejeter le DSC comme mesure dans les études du vieillissement cognitif.

Toutefois, pour étudier l'effet d'exercice sur la cognition, la mesure la plus importante était celle d'oxygénation (par SRT par exemple). Au moment de faire notre étude, les systèmes de SRT n'étaient pas disponibles commercialement, mais il apparaît plausible que de tels systèmes seront développés (malgré que leur coût demeure élevé) tout comme les systèmes d'IOD le sont maintenant. La mesure SRT ne nécessite qu'une dizaine de minutes au total et permet d'isoler une source de variabilité dans les études utilisant l'IOD pour comparer des groupes.

Le but de cette étude n'était pas de vérifier ou réfuter les hypothèses de la littérature sur l'interaction entre vieillissement, cognition et condition cardiorespiratoire, mais plutôt d'en approfondir les explications possibles en explorant leurs corrélats vasculaires. Néanmoins, nous pouvons affirmer que nos résultats cadrent partiellement avec deux grandes hypothèses sur le vieillissement. D'une part, l'hypothèse du vieillissement frontal stipule que le lobe frontal et les fonctions exécutives qui en relèvent seraient particulièrement affectées par le vieillissement (Greenwood, 2000a). Nos données ont effectivement montré que les régions principales de

diminution du DSC étaient frontales, tout comme celles où diminuait la connectivité du réseau du mode par défaut. Un effet d'interaction âge x condition dans le taux d'erreurs dans la tâche Stroop signifie aussi que la capacité d'inhibition des stimuli incongruents était plus affectée chez les âgés. Par contre, cet effet n'a pas été observé dans les temps de réaction.

D'autre part, la seconde grande hypothèse de la littérature liée à notre étude est celle de l'effet de l'exercice physique sur la cognition chez les personnes âgées. Nos résultats sont en accord avec cette dernière. En effet, nous avons détecté un effet d'interaction âge x condition cardio-respiratoire dans les temps de réaction à la tâche Stroop, indiquant que les personnes âgées en bonne forme physique exhibaient une meilleure performance cognitive. Notons que ces résultats ne permettent pas de *prouver* l'hypothèse puisque plusieurs autres facteurs pourraient expliquer la corrélation de la forme physique avec la cognition (saines habitudes de vie, santé générale, motivation, etc.). Certaines études longitudinales de la littérature ont toutefois conclu à un lien de cause à effet (Dustman et al., 1984; Kramer et al., 1999).

Certaines limitations de techniques de mesures ont été mises en évidence lors de cette étude. Nous avions initialement inclus des mesures d'IOD durant la tâche Stroop, mais n'avons pas pu les utiliser pour comparer les groupes puisqu'elles ne démontraient pour la plupart pas d'activation claire. L'IOD ainsi que l'ASL n'ont donc pas été des outils utiles dans l'étude d'une tâche subtile comme la tâche de Stroop. Si c'était à refaire, je limiterais l'utilisation en imagerie fonctionnelle de ces techniques à des tâches robustes telles que de forts stimuli visuels ou l'hypercapnie (quoique plusieurs données préliminaires ont mis en doute la capacité de mesurer la réponse à l'hypercapnie en IOD). L'application de l'IOD aux nouveau-nés (Lin et al., 2013) est aussi prometteuse puisque ces sujets ont une tête plus transparente et ne sont pas des candidats pour l'IRMf.

7.3 Troisième objectif

L'objectif du troisième article était d'investiguer les effets de l'âge sur plusieurs composants de la réponse hémodynamique à un stimulus principalement vasculaire, l'hypercapnie. Nous avons mesuré des réponses en débit, en HbT et en HbO qui étaient plus faibles chez les âgés, tandis que le ratio $\Delta CBV/\Delta CBF$ était aussi plus faible. Ces observations corroborent une des hypothèses centrales de cette thèse, soit que le vieillissement a des manifestations purement vasculaires

(mesurées ici avec un stimulus indépendant de l'activité neurale) responsable d'une part des différences mesurées en neuroimagerie. Une plus faible augmentation de débit en réponse à l'hypercapnie peut indiquer une plus faible réactivité vasculaire (Lu et al., 2011), ce qui veut dire une plus faible réponse vasculaire en réponse à un agent vasodilatateur. La diminution du ratio ΔCBV/ΔCBF suggère, dans l'interprétation du modèle du Ballon (R B Buxton et al., 1998), une diminution du gonflement des vaisseaux par l'influx sanguin.

Nos données suggèrent donc qu'avec le vieillissement, les vaisseaux sanguins diminuent leur dilatation à la fois passive et active, deux mécanismes qui pourraient relever de mécanismes très différents. En effet, la réactivité vasculaire qui décrit l'augmentation des vaisseaux en réponse aux stimuli est liée aux mécanismes de signalement du couplage neuro-vasculaire, tandis que la dilatation passive relèverait du gonflement élastique des vaisseaux lorsque la pression et le débit sanguins augmentent. Des travaux de modélisation dans la lignée de ceux de Behzadi et Liu (Behzadi & Liu, 2005), ainsi que des mesures *in vivo* de la pulsatilité des vaisseaux (Santisakultarm et al., 2012), seraient des étapes à suivre pour explorer cette hypothèse. La MBP permet de suivre les modifications du débit et du volume en réponse aux pulsations du cycle cardiaque et en réponse à la stimulation (comme dans les travaux de Santisakultarm et al.), et cette avenue fait partie des travaux du futur proche de notre laboratoire.

Encore une fois, dans cette étude, l'anesthésie a pu jouer un rôle confondant en influençant les valeurs de base du débit et du volume sanguin (Todd & Weeks, 1996). Si l'anesthésiant n'était pas métabolisé de la même façon chez les rats âgés, cela aurait pour effet de biaiser les mesures des changements relatifs de débit et des autres variables. Une étude sur les effets de l'anesthésiant en fonction de l'âge pourrait éclairer ces questions.

7.4 Conclusions générales

En combinant les observations des trois études, nous pouvons proposer de nouvelles hypothèses sur les mécanismes du vieillissement cérébral. La diminution d'HbT régionale mesurée chez l'humain pourrait refléter l'effet combiné de la diminution de la densité de capillaires et de l'hématocrite. L'hématocrite plus faible dans les capillaires pourrait expliquer la diminution de l'oxygénation (sO_2) des tissus à l'échelle macroscopique, puisque les globules rouges sont responsables du transport de l'oxygène. En outre, la vitesse accrue des globules rouges pourrait

aussi défavoriser la diffusion d'oxygène du sang vers les tissus en diminuant le temps de transit, tel que discuté dans le premier article. Il serait intéressant alors d'étudier l'effet de l'exercice physique sur l'hématocrite et la vitesse des globules rouges chez les sujets âgés, afin de vérifier si l'effet observé de l'exercice sur l'oxygénation est médié par un effet sur ces deux variables. Un projet futur intéressant serait une étude longitudinale des effets de l'exercice chez le rat. Il faudrait alors entraîner les rats en exercice cardiorespiratoire. À l'Institut de Cardiologie de Montréal, nous avons accès à un système de tapis roulants faits pour permettre aux rats de courir à vitesse contrôlée. Il faudrait alors utiliser une méthode d'imagerie non-terminale afin de pouvoir prendre des mesures avant et après l'entraînement. Dans le cadre de la première étude, nous avions initialement planifié d'entraîner la moitié des animaux, mais le nombre de rats survivant au moment de débuter l'étude nous a forcés à changer de plan. Pour faire une étude d'entraînement, il faudra planifier un grand nombre d'animaux et commencer l'entraînement à un âge plus jeune (18 mois par exemple dans le cas des rats Long-Evans).

7.5 Retombées et impacts

Cette thèse cherchait à fournir une interprétation plus limpide et quantitative des mesures hémodynamiques dans le vieillissement, qui sont à ce jour largement utilisées dans la recherche en neurosciences. En outre, ce projet innovait en proposant d'exploiter des mesures hémodynamiques non seulement comme miroir de l'activité neuronale, mais aussi pour caractériser la santé vasculaire cérébrale. Les mesures *in vivo* du débit sanguin dans un grand nombre de capillaires cérébraux de rats âgés sont, à notre connaissance, tout à fait nouvelles dans la littérature et permettent de répondre à des questions fondamentales sur l'effet du vieillissement sur l'apport sanguin au cerveau. La combinaison d'imagerie BOLD avec des mesures du débit, d'HbO, HbR et HbT ainsi que de mesures microscopiques est aussi novatrice et permet d'avancer vers une meilleure compréhension des effets du vieillissement sur le très populaire signal BOLD. L'étude chez l'humain était la première à établir un lien direct entre une mesure de l'oxygénation cérébrale et la cognition ainsi que la santé cardiorespiratoire. Les résultats pourraient avoir des retombées sur la santé publique, en contribuant à l'avancement d'un domaine de recherche qui justifie des recommandations sur la santé cardiovasculaire des personnes âgées.

CONCLUSION ET RECOMMANDATIONS

Dans cette thèse, plusieurs techniques d'imagerie cérébrale basées sur l'hémodynamique à différentes échelles spatiales ont été utilisées pour étudier les effets du vieillissement sur le cerveau. Les conclusions principales sont les suivantes. Le débit sanguin cérébral régional diminue avec l'âge, toutefois cette diminution semble attribuable surtout à une baisse de la densité des capillaires puisqu'une augmentation du débit dans les capillaires individuels a été observée. Il reste à vérifier ce résultat chez l'animal non-anesthésié. Une diminution de l'hématocrite dans les capillaires individuels avec l'âge a aussi été observée ainsi qu'une baisse de l'oxygénation régionale, qui chez les individus âgés semble être inversement corrélée à la santé cardiovasculaire ainsi qu'à la performance cognitive. Enfin, la réponse héymodynamique à l'hypercapnie diminue avec l'âge, mais cette diminution est plus grande pour la réponse en volume sanguin que celle en débit. Cette différence dans la relation débit-volume pourrait indiquer une perte de compliance des vaisseaux avec l'âge. Il serait intéressant d'explorer le lien entre le diamètre des vaisseaux et leur dilatation qui est fonction de cette compliance.

Les résultats de cette thèse démontrent une fois de plus l'importance de mesurer et de contrôler les variables hémodynamiques dans les études du vieillissement et de toute condition ou pathologie susceptible d'affecter la physiologie de base. Il serait recommandable que toutes les études IRM fassent usage d'une mesure du débit sanguin cérébral de base, par exemple en utilisant une séquence d'ASL. Pareillement, les études d'imagerie optique qui disposent d'un appareil de SRT devraient systématiquement l'employer afin d'obtenir des mesures de l'état de base en plus des changements évoqués par les stimuli.

Les modèles animaux tel que le rat utilisé dans cette thèse sont un outil précieux dans l'étude de phénomènes complexes dont dépend fortement l'interprétation des résultats obtenus chez l'humain. Pour améliorer la translation des résultats à l'humain, l'utilisation de méthodes permettant d'éviter l'anesthésie serait souhaitable. Les études futures faites chez l'animal gagneraient aussi à combiner les mesures microscopiques avec une mesure macroscopique du débit afin de pouvoir directement établir le lien entre les deux échelles et ainsi maximiser l'impact sur la recherche humaine. À long terme, une meilleure compréhension des mécanismes du vieillissement pourrait permettre d'améliorer le diagnostic des maladies associées, d'en mieux cibler les traitements et même de retarder ses effets, Graal de la médecine moderne.

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ANNEXE 1 – Accusé de réception du premier article

Neurobiology of Aging

Ms. No.: NBA-13-681

Title: Aging-related differences in cerebral capillary blood flow in anesthetized rats

Corresponding Author: Ms. Michèle Desjardins

Authors: Romain Berti; Joël Lefebvre; Simon Dubeau; Frédéric Lesage

Dear Ms. Desjardins,

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ANNEXE 2 – Accusé de réception du deuxième article

Ms. No.: NIMG-13-2364

Title: Association of cardiovascular fitness with cognition, cerebral blood flow and oxygenation in aging

Corresponding Author: Ms. Michèle Desjardins

Authors: Philippe Pouliot; Vincent Perlbarg; Laurence Desjardins-Crépeau; Claudine Gauthier; Paul-Olivier Leclerc; Richard D Hoge; Louis Bherer; Habib Benali; Frédéric Lesage

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